Abdominal massage plus advice, compared with advice only, for neurogenic bowel dysfunction in MS: a RCT

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Randomised controlled trial, process evaluation and economic analysis comparing abdominal massage plus advice to advice only for neurogenic bowel dysfunction

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Key words: Neurogenic bowel dysfunction, Constipation, Abdominal massage, Multiple sclerosis, Bowel, Stool, Trial, Process Evaluation

Abstract

Background: 50-80% of people with multiple sclerosis (PwMS) experience neurogenic bowel dysfunction (NBD - constipation and faecal incontinence) which impacts on quality of life and can lead to hospitalisation.

Objectives: To determine the effectiveness and cost effectiveness of abdominal massage plus advice on bowel symptoms on PwMS compared to advice only. A process evaluation investigated factors that impacted upon effectiveness and possible implementation.

Design: A randomised controlled trial with process evaluation and health economic components. Outcome analysis was undertaken blind.

Setting: 12 UK hospitals
in the

Participants: PwMS who had 'bothersome' NBD

Intervention: Following individualised training, abdominal massage was undertaken daily for 6 weeks (Intervention Group). Advice on good bowel management as per the MS Society Advice Booklet was provided to both groups. All participants received weekly telephone calls from the research nurse.

Main Outcome Measures: The primary outcome was the difference between the Intervention and Control Groups in change in the Neurogenic Bowel Dysfunction (NBD) Score from Baseline to Week 24. Secondary outcomes were measured via a bowel diary, adherence diary, the Constipation Scoring System, patient resource questionnaire and the EQ-5D-5L.

Results: 189 participants were randomised (99 in the control and 90 in the intervention group) and intention-to-treat analysis performed. Mean age was 52 years (SD 10.83), 81% (n=154) were female, 11% (n=21) were wheelchair dependent. Fifteen from the Intervention Group and five from the Control Group were lost to follow up.

The change in NBD Score by Week 24 demonstrated no significant difference between Groups (mean difference total score -1.64, 95% CI -3.32 to 0.04, p=0.0558); there was a

significant difference between groups in change in the frequency of stool evacuation per week (mean difference 0.62, 95% CI 0.03 to 1.21, p=0.039), and in the number of times per week participants felt they emptied their bowels completely (mean difference 1.08, 95% CI 0.41 to 1.76, p=0.002) in favour of the Intervention Group.

Three-quarters of participant interviewees reported benefits e.g. less difficulty passing stool, more complete evacuations, less bloated, improved appetite, and 85% continued with the massage. A cost utility analysis conducted from an NHS and patient cost perspective found in the imputed sample with bootstrapping a mean incremental outcome effect of the intervention relative to usual care of -.002 QALYs (95% CI -.029 to .027). In the same imputed sample with bootstrapping the mean incremental cost effect of the intervention relative to usual care was £56.50 (95% CI -372.62 to £415.68).

No adverse events were reported. Limitations include unequal randomisation and drop-out, and the possibility of ineffective massage technique.

Conclusion: The increment in the primary outcome favoured the intervention group but it was small and not statistically significant and the economic analysis identified that the intervention was dominated by the control group. Given the small improvement in the primary outcome, but not in terms of QUALYS, a low cost version of the intervention might be considered worthwhile by some patients.

Future Work: Research is required to establish possible mechanisms of action and modes of massage delivery.

497 words

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List of Abbreviations

AE	Adverse Events
AHP	Allied Health Professions
ARC	Anne Rowling Clinic
BMI	Body Mass Index
BNF	British National Formulary
BR	Resource use with bowel problems
CCGs	Clinical Commissioning Groups
CI	Chief Investigator
CMO	Context, mechanism and outcome
Cons Med	Concomitant Medication
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CSS	Constipation Scoring System
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DMEC	Data Monitoring and Ethics Committee
DMT	Disease modifying treatments
EQ-5D-5L	EuroQol five-dimension questionnaire
FI	Faecal Incontinence
GCU	Glasgow Caledonian University
GPs	General practitioners
HCPs	Healthcare professionals
HR	Resource use with health problems
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
ISRCTN	International Standard Randomised Controlled Trial Number
JRH	John Radcliffe Hospital
LCH	Leeds County Hospital
LIN	Lincoln County Hospital
MRC	Medical Research Council
MS	Multiple Sclerosis
NBD	Neurogenic Bowel Dysfunction
NBD-PROM	Neurogenic Bowel Disorder patient-reported symptom and quality of life questionnaire
NBDS	Neurogenic Bowel Disorder Score
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NGH	Northampton General Hospital
NHiS	Healthcare Intelligence and Commissioning Excellence
NHS	National Health Service
NIHR	National Institute for Health Research

NMAHPH RU	Nursing, Midwifery and Allied Health Professionals Research Unit
PI	Principle Investigator
PICs	Patient Identifying Centres
PIL	Patient Information Leaflet
PMG	Project Management Group
PT	Preferred Term
PwMS	People with Multiple Sclerosis
QALY	Quality Adjusted Life Years
RCN	Royal College of Nursing
RCT	Randomised Controlled trial
REC	Research Ethics Committee
RHH	Royal Hallamshire Hospital
RPH	Royal Preston Hospital
RVH	Royal Victoria Hospital
SAE	Serious Adverse Event
SD	Standard Deviation
SGH	Southern General Hospital
SOC	System Organ Class
SOP	Standing Operating Procedure
SRH	Salford Royal Hospital
STARD	Standards for Reporting of Diagnostic Accuracy
TCTU	Tayside Clinical Trials Unit
TSC	Trial Steering Committee
TWC	Thomas Walton Centre
UCH	University College Hospital
UK	United Kingdom
UK-CRC	UK Clinical Research Collaboration

Plain English Summary

The symptoms of neurogenic bowel dysfunction (NBD) are constipation, and/or faecal incontinence, and is common in people with Multiple Sclerosis (PwMS) affecting quality of life. The AMBER study aimed to find out whether abdominal massage improved the symptoms of NBD in PwMS.

191 eligible participants, who felt their constipation was "bothersome", were allocated randomly to either: –

- advice on the management of bowel dysfunction (Control group; 100 participants) or
- advice and abdominal massage (Intervention group; 91 participants).

Quality of Life questionnaires and a bowel diary were completed by all participants at the start of the trial, at the end of 6 weeks of intervention and again at 24 weeks. To further assess the intervention 20 participants had telephone interviews at the beginning and end of the trial.

Researchers wanted to know if participants in the Intervention group had an improvement in their bowel symptoms when compared to the Control Group at Week 24.

At the end of the study, the main symptom questionnaires showed a slight, but not statistically significant, improvement in the Intervention group (not much difference between groups) and our economic analysis showed it was more expensive. However, at the end of the study participants in the Intervention Group did register some important findings; they: –

- passed stools more frequently,
- felt they emptied their bowel more completely
- generally took less laxatives,
- felt better

The interviews also identified that participants liked: –

- the fact drugs were not involved
- they could do the massage themselves
- the lack of adverse side effects.

Given the small improvement in the primary outcome but not in terms of cost-effectiveness, a low cost version of the intervention e.g. as part of a self-management pathway, might be considered by some patients.

285 Words

Scientific Summary

Background

Multiple Sclerosis has an increasing prevalence in the United Kingdom (UK) and is the most common neurological condition in young adults affecting over 100,000 people at present. It is estimated that 60% of people with multiple sclerosis (PwMS) have problematic neurogenic bowel dysfunction (NBD). NBD is rated as one of the most devastating scenarios affecting these patients and includes the symptoms of constipation, faecal incontinence (FI), evacuation difficulties or a combination of these. Constipation can lead to the individual becoming housebound, spending hours trying to empty their bowels and limiting their ability to work; whilst FI is often described as the most devastating event imaginable leading to social and emotional issues. Management of NBD in PwMS has been under-explored and lacks supporting evidence. It is costly both in terms of carer and patient time and to the NHS. People with MS have 2-3 times more admissions to hospital for bowel complications than those without MS. People with MS use laxatives, suppositories, prolonged digital rectal stimulation and/or rectal irrigation but often these interventions have inconsistent results. Abdominal massage is a minimally invasive modality potentially stimulating gut motility. A Cochrane review reported significant benefits in the reduction of the symptoms of constipation in several small trials with heterogeneous populations. Abdominal massage may offer a new option in the pathway to treat NBD.

Objectives

The aim of this study was to assess the clinical and cost effectiveness of adding abdominal massage to the provision of advice calls compared to advice only, with both groups being supported by weekly telephone calls. We also aimed to identify and investigate the mediating factors that impacted upon effectiveness and possible implementation via a Process

Evaluation sub-study and pilot transit and ano rectal physiological sub-study to identify possible mechanisms of action.

All outcomes were undertaken at Baseline, Week 6 and 24

Primary Outcome

The difference in change between the Intervention and Control Groups in the Neurogenic Bowel Dysfunction (NBD) Score from Baseline to Week 24.

Secondary Outcomes

Change in the Constipation Scoring System (CSS) from Baseline to Week 6 and 24

Information from the study trial specific 7-day bowel diary (recorded at Baseline, weekly during the 6 weeks of intervention, and during Week 23).

Bladder Dysfunction as measured by the Qualiveen Short Form Questionnaire

Quality of Life as measured by the EQ-5D-5L, and by a novel Neurogenic Bowel Disease questionnaire

Resource use as collected by a Patient Resource Questionnaire

Bowel transit and ano rectal physiological tests (one centre only) undertaken pre intervention and at Week 24

Other outcomes recorded at each telephone conversation

Change in medication

Adverse events

Process Evaluation Outcomes

Qualitative interviews with 20 participants were conducted before and after undertaking the intervention (n=40).

Interviews with health care professionals (HCP) (n=25) involved in the delivery of the trial shortly after starting the study and/or at study end (n=42).

Interviews with 6 key stakeholders involved with incontinence policy or services for PwMS at one stage only (n=6).

Methods

The study was a UK-based multi-centre pragmatic parallel-group randomised controlled trial. There was 1:1 allocation between the groups with stratification by site and minimisation on level of disability.

Eligibility was being 'bothered' by bowel symptoms.

Inclusion

- Male or female over the age of 18 years.
- Diagnosis of MS (no MS relapse for 3 months).
- No major change of medication for 1 month.
- Not used abdominal massage in the previous 2 months.

Exclusion

- Unable to undertake the massage themselves and did not have a carer willing to do it.
- Unable to understand the study processes in order to give informed consent.
- Contraindications to abdominal massage, e.g. abdominal/pelvic cancer; hiatus, inguinal or umbilical hernia; rectal prolapse; inflammatory bowel disease; abdominal scars, abdominal wounds or skin disorders.
- Pregnant.

After assessment for eligibility and completion of informed consent each participant was scheduled for one study visit for collection of baseline data. Details were inputted into a bespoke database held at Dundee Clinical Trials Unit, which facilitated immediate on screen randomisation with allocation concealment. All participants were provided with the Multiple Sclerosis Society Booklet on bowel management. Those in the Intervention Group additionally received instruction in undertaking the massage (Self or carer), had the massage demonstrated on them and they or their carer were given the opportunity to ask questions and undertake supervised practice. A DVD showing the massage and 2 leaflets outlining it were also provided. Participants were recommended to undertake the massage daily for approximately 10 minutes.

Sample size for the RCT was based on the NBD score using data from a pilot study. Sixty per group was calculated as necessary to detect a difference between groups of 4.21 (standard deviation, SD 7.02) at a 5% level of significance with 90% power. Thus, for a fully powered study, the total sample size, allowing for a 20% drop-out, was 150. However, in response to suggestions from the funding body, the sample size was increased to 200 (100 per group), which allowed for greater attrition.

Ethical approval for the study was granted by the West of Scotland Research Ethics Committee 4, on the 11th June 2014 (reference number 14/WS/0111). A total of 11 NHS Trusts/Health Boards granted 12 local NHS site recruitment approvals (two different hospitals belonged to 1 trust). The study sponsor was Glasgow Caledonian University (GCU) and the AMBER trial office was based in the Nursing, Midwifery and Allied Health Professions Research Unit (NMAHP-RU) at GCU.

Statistical Analysis

Categorical data are presented using counts and percentages, continuous variables are presented using mean+/-standard deviation and absolute differences with 95% confidence

intervals. Data for continuous outcome measures (both primary and secondary) were assessed for normality prior to analysis. Transformations of the outcome variables were used where necessary if these were not normally distributed.

If data were normally distributed, outcome measures were assessed by multiple linear regression. The primary analysis consisted of comparisons between treatment groups (bowel massage versus no massage) at the final visit (Week 24), adjusted for site, minimisation on level of mobility (walking unaided, aided or wheelchair bound) as well as baseline measure of the outcome, and gender.

In a secondary analysis of the primary outcome, baseline variables age, gender, Body Mass Index, BMI, type of MS, site disease duration (years since diagnosis), cognitive symptoms of MS and minimisation variable level of mobility (walking unaided, aided or wheelchair bound) was included in the model.

Where data were not normally distributed and could not be transformed into a normal distribution, data were analysed using non-parametric methods in addition to multiple linear regression.

In addition to the comparison of Baseline versus Week 24, a repeated measures analysis was performed on the outcomes using all available visits.

Data for categorical outcome measures were assessed by logistic regression in the same way as described for continuous outcome measures.

Statistical significance was taken as two-sided p=<0.05.

Results

Three hundred and eighty-nine patients were given information about the study, 273/389 (60.9%) were screened and 191 (48.1%) randomised, 90 (47.1%) allocated to Intervention and 100 (51.8%) to Control. The number of participants per site ranged from 9-26 (median 16 patients). Twenty-two of the randomised participants did not complete the study. Two of

these were post randomisation exclusions (essentially randomised in error) and data were not collected from these participants, leaving 189 for analysis. Fifteen in the Intervention Group and 5 in the Control Group withdrew or were lost to follow-up. The missingness of any data appeared to be at random with no obvious bias.

Baseline

Eighty-one per cent (154/189) of participants were female, with a mean age of 53 years (range 26–79 years). Mean duration of multiple sclerosis was 14.3 years (range 0 years to 51 years). Demographics and clinical symptom profiles of the two groups were evenly matched. Bowel symptoms had commenced more than 10 years ago in 37% and less than one year in 4%. The main bowel symptoms reported by participants at baseline were feelings of incomplete emptying, straining to pass stool, and bloating.

Primary Outcome (NBD)

At Baseline, the total score for the NBD Intervention arm was Mean 7.6 (SD 5.31) and in the Control Arm 8.6 (SD 5.08) and at Week 24 it was 7.4 (SD 5.23) for the Intervention Group and 8.7 (SD 5.70) for the Control Group. The mean difference in change between groups was not statistically significantly different for the Total Score in our Primary outcome measure at 24 weeks -1.61 (CI 95% -3.32, 0.04) p=0.0558.

Secondary Outcomes (Primary analysis)

The Intervention Group had a Total Mean CSS score of 11.7 (SD 4.05) and the Control Group had a mean CSS score of 11.5 (SD 3.77) at Baseline and at Week 24 the Intervention Group had a Mean score of 10.1 (SD 4.10) and Control Group 11.1 (SD 3.91). There was no significant mean difference in change between groups on the Total Score of the CSS at Week 24: -0.88 (CI-2.03,0.27) p=0.1308.

There were virtually no differences between the two arms either at baseline or post treatment in the Qualiveen Short Form Bladder questionnaire or in the EQ-5D-5L,

In our feasibility study on mechanistic evaluation, the low numbers (n=11/23) that completed the transit study and ano-rectal physiology tests make it impossible to undertake meaningful analysis on differences between groups. However, just over 60% of all participants demonstrated slow colonic transit at baseline.

Bowel Diary

Frequency of Evacuation - The Mean frequency of stools passed per week at Baseline in the Intervention Group was 3.9 (SD1.68) and for the Control Group it was 4.0 (SD 1.74). At Week 24, the Intervention Group was 4.3 (SD 1.88) and the Control Group 3.9 (SD 1.89). This was a significant mean difference in change between the groups of 0.62 (CI0.03,1.21) p=0.039.

There was no significant difference in the mean change between groups on time spent on the toilet or number of attempts to pass stool at Week 24 -3.35 (CI-23.1,16.4) p=0.7377 and 1.14 (CI 0.92-3.19) p=0.2770 respectively.

There was a significant difference in the mean change between groups on the number of times the participants felt that they had successfully emptied their bowel at Week 24: 1.08 (CI 0.41,1.76) p=0.002, with the Intervention Group showing greater effect.

Using repeated measures analysis statistically significant results also were found for the number of stools passed per week and the number of times participants felt their bowels to be emptied at Week 6 (odds ratio 0.98, 95% CI 0.36 to 1.61; p=0.039) and (odds ratio 0.56 95% CI 0.03 to 1.10; p=0.039) with the Intervention Group showing greater effect. However, this effect was decreased for both outcomes at Week 24.

There is also some evidence that the laxative use at Week 24 was twice as likely to be lower in the Intervention Group than the Control Group OR = 2.37 (95% CI 0.87, 6.46), p = 0.092

Other outcomes

Regression analysis indicates a greater response in the Intervention Group for those walking unaided or aided compared to those using a wheelchair. Those of greater age and higher BMI also did slightly better. Duration of MS did not seem to be important but those with relapsing

remitting MS responded better than those with primary or secondary progressive MS. Cognition severity indicated that those with mild or no impairment did better than those with severe impairment. Consistent with other findings males did significantly better than females (odds ratio -2.789, 9% CI -5.179 to -0.399; p=0.0226).

Serious adverse events

There were nine SAEs and none were related to the trial and all were resolved.

Process Evaluation

Twenty intervention participants were interviewed twice: at baseline and at the end of the intervention period. The recordings were transcribed and supported by QSR NVivo (v10). All 20 completed the study, with 15 reporting benefits such as increased frequency of stools and feeling complete evacuation more often. Other benefits not recorded by trial measures represented important improvements in quality of life for participants, including: increased appetite, energy, better sleep and greater control over bowel function. Participants shared their experiences of administering the massage, including solutions they devised to manage any difficulties. Comparison with change in our primary outcome measure identified inconsistencies in what the participant was saying in the interviews and change in Total Score. For the 5 who felt there was no change to their bowel habits, analysis of their bowel diaries and interviews gave some indication why the treatment may not have worked for them: they had an ideal stool type at baseline; they struggled to administer the massage due to poor dexterity, fatigue and weakness. Eighteen interview participants reported that they would continue with the massage beyond 24 weeks. The HCP interviewees (n=25) were involved with recruitment and had been trained in delivering the massage intervention. Most reported that recruitment of study participants was aided by the fact that this was a non- pharmacy intervention and could be performed by the participant themselves. The 6 stakeholders identified there was a lack of evidence based interventions for patients with NBD and potentially, abdominal massage could offer a safe, non-expensive additional option for managing bowel problems.

Economic Evaluation

A cost utility analysis was conducted from an NHS and patient cost perspective. The mean incremental cost for the Intervention Group compared to the Control Group was £56.50 (95% CI -372.62 to £415.68). The incremental gain in Quality Adjusted Life Years (QALYs) was -.002 QALYs (95% CI -.029 to .027). Given these results the intervention appears to be dominated by the control group.

Conclusions

Abdominal massage is a non-invasive, non-pharmacological intervention. Although the increment in the primary outcome favoured the intervention group it was small and not statistically significant and the economic analysis identified that the intervention was dominated by the control group. Given a small improvement in the primary outcome but not in terms of QUALYs, a low cost version of the intervention e.g. as part of a self-management pathway, might be considered worthwhile by some patients. Some secondary outcomes were in favour of the intervention and reached statistical significance with 15/20 interviewees reporting improvements.

Further research is required to further establish validated outcome measures in this population as well as further mechanistic investigations.

Trial registration

The study was registered with the International Standard Randomised Controlled Trial register (ISRCTN 85007023) and on Clinical Trials.Gov (NCT03166007).

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CHAPTER 1 Introduction

Scientific Background

Multiple Sclerosis has an increasing prevalence in the United Kingdom (UK) and is the most common neurological condition in young adults (average age of onset 34 years) affecting over 100,000 people at present.[1] It is estimated that 60% of people with multiple sclerosis (PwMS) have problematic neurogenic bowel dysfunction (NBD)[2] and increased life expectancy rates, due to advances in healthcare, presents the additional challenges of the ageing bowel.[3] NBD is rated as one of the most distressing scenarios affecting these patients and includes the symptoms of constipation and faecal incontinence (FI).[4] Constipation can lead to the individual becoming housebound, spending hours trying to empty their bowels and limiting their ability to work; whilst FI is often described as the most devastating event imaginable, leading to social and emotional issues.[5] An 'MS Trust' report published in April 2017 identified that emergency admissions (many thought to be preventable) to hospital for PwMS have increased by 12.7% over the two years 2015/16, with overall admissions for bladder and bowel related issues e.g. impaction, costing £10.4m in 2015/16.[6]

Aetiology of Neurogenic Bowel Dysfunction

Aetiology of bowel dysfunction in PwMS is multifactorial; reduced mobility and polypharmacy may have a contributory causative role. Coincidental pelvic nerve lesion occurring during childbirth could also contribute to faecal incontinence in women with MS.[7] Spinal cord lesions appear to be most important in the pathogenesis of NBD symptoms in MS[8]. The pathways of neural control of defecation are not fully defined; however, cortical and pontine centres may play a pivotal role in the regulation of sacral segments.[8,9]

Conduction times of central motor pathways to sphincteric sacral neurons and pelvic floor striated muscle have been shown to be prolonged in MS.[10] Impaired anorectal sensation may also contribute to the symptoms: somatosensory evoked potentials were delayed in PwMS compared to controls in one study.[11] Loss of central modulation on spinal cord segments may lead to sympathovagal imbalance: this can lead to constipation, characterised by lengthened colon transit time.[12] Constipation has thus been attributed to rectal outlet obstruction, absent or incomplete puborectal, anal canal and sphincter musculature relaxation and prolonged

colonic transit time.[10,13] Regarding faecal incontinence, studies have described reduced sensation of rectal filling, reduced rectal compliance, low anal sphincter pressures and hyper-reactivity of the rectal wall. The coexistence of faecal incontinence and constipation can be explained by in-coordinated action of the external/internal anal sphincter during expulsion; poor pelvic musculature relaxation may cause incomplete emptying of the rectum, which precipitates faecal incontinence when anal sphincter weakness and anorectal hyposensitivity are present.[14,15]

Current treatment/management options

Management of NBD in PwMS has been little explored and lacks supporting evidence.[17] It is costly both in terms of patient time and to the NHS (e.g. people with MS have 2-3 times more admissions to hospital for bowel complications than non-MS patients).[16] It also has an impact on the families and carers of PwMS.[18] People with MS use laxatives, suppositories, prolonged digital rectal stimulation and/or rectal irrigation but often these interventions have inconsistent results. For example, one patient in our previous study would take laxatives two evenings per week, but then could not leave the house the next day as he had no control over when he would pass stool.[5]

Evidence for the effectiveness of abdominal massage for constipation

A Cochrane Systematic Review, 'Abdominal massage for the treatment of chronic constipation' has been undertaken to determine the effects of abdominal massage for the relief of symptoms of chronic constipation in comparison with no treatment or other treatment options.[19] Nine randomised controlled trials (12 randomised comparisons) involving 427 participants were included. The study populations were small with a maximum of 32 per group, heterogeneous and all had moderate to high risk of bias. Findings from two trials suggest that abdominal massage compared to advice from a physician provided significant additional relief of symptoms from constipation in the short term. Two trials found no significant differences between groups. One trial which had the 3 groups of aroma massage, plain massage and control reported that both the aroma massage group and the plain massage group had improved quality of life. The review concluded that there was

insufficient data to allow reliable conclusions to be drawn on the effects of abdominal massage in the management of constipation. There was some evidence to suggest that there might be a therapeutic effect; however, larger, more rigorous trials are required to provide evidence of both the effectiveness and cost effectiveness of abdominal massage.

How the intervention might work

There is some evidence to suggest that abdominal massage will reduce colonic transit time and enable predictable complete evacuation; however, the possible mechanism of action is not yet fully understood.[20,21,22] The function of the gastrointestinal tract is influenced by, among other things, activity in the parasympathetic division in the autonomic nervous system. Stimulation of the parasympathetic division increases the motility of the muscles, increases the digestive secretions, and relaxes sphincters in the gastrointestinal canal.[23,24,25] Massage is thought to stimulate peristalsis in the gut by producing rectal muscular waves that stimulate the somato-automatic reflex and initiate bowel sensation, so reducing colonic transit time.[26] Furthermore, the active massaging action may result in a softening of stool consistency, allowing the stool to be passed more easily.[27]

Development of the intervention

The abdominal massage intervention used within this trial was based on massage as formally taught in physiotherapy training within the UK and used by an expert in the area in earlier studies.[28,29,30] This expert was involved in the development of the training materials and in the training of the clinicians undertaking the massage. All clinicians involved with teaching the massage to participants underwent half a day's training in the massage technique, as well as presentations on NBD and good bowel care. Information provided to participants on bowel care was based on the MS Society's handbook on bowel management. A description of the intervention has previously been published.[31.] Copies of the training materials and MS Bowel Handbook are attached to this report (Appendices 1 and 2).

Who delivers the intervention

In previous studies, the massage was delivered by a health care professional with experience in massage, a family carer or by the patient themselves. It was discovered, however, that the amount of training and support received by participants is poorly described. In this trial, the massage was designed and taught to be either self-massage or undertaken by a 'carer.' Likewise, the training of the 'trainers' (healthcare professionals involved in seeing the patient

and teaching the massage) was such that it was delivered in a half-day session, but also required individuals to undertake further practice to consolidate their training. If this limited training plus support materials for HCPs and patients proves effective, then the abdominal massage can potentially be implemented in many settings to patient populations who experience constipation.

Hypothesis

A 6 week intervention of abdominal massage and bowel management advice (Intervention Group) will improve symptoms and quality of life in PwMS who have bowel dysfunction compared to those who receive advice alone (Control Group).

Chapter 2: Trial Design and Methods

Design

The AMBER trial was designed to evaluate whether abdominal massage was an effective treatment in reducing the symptoms of Neurogenic Bowel Dysfunction, particularly constipation, in people with MS (PwMS). This trial was a multi-centre, patient randomised, superiority trial comparing the following: an intervention of optimised bowel care with once daily abdominal massage for 6 weeks against the control of optimised bowel care without massage in PwMS who have stated that their constipation is bothersome. A description of the trial protocol has already been published.[31]

The main trial was supported by a process evaluation to explore the possible mediating factors that may impact upon the effectiveness of the intervention, how these mediating factors influence effectiveness, and whether the factors differ between the randomised groups. Trial processes were evaluated to provide evidence of potential importance in the future implementation of the intervention (see Chapter 5).

The main study objectives were;

1. To establish if an optimised bowel care programme (i.e. provision of advice/information on bowel management) with abdominal massage, compared to an optimised bowel care programme alone, is more effective and cost-effective in reducing the symptoms of NBD at Week 24 in people with MS.
2. To identify and investigate via a process evaluation the possible mediating factors that impact upon the effectiveness of the intervention (including intervention fidelity), how these mediating factors influence effectiveness, and whether the factors differ between the randomised groups (Chapter 5).
3. To undertake a formal economic evaluation of the interventions from an NHS and the patient perspective (Chapter 4).

4. To undertake a feasibility study relating to the mechanisms of action using anal manometry and colonic transit tests at one tertiary bowel centre where these tests are routinely undertaken.
5. To record data to validate responsiveness to treatment of a quality of life questionnaire on NBD.

Ethical approval and research governance

Ethical approval for the trial was granted by the 'West of Scotland Research Ethics Committee 4' on the 11th of June 2014 (reference number 14/WS/0111). NHS approval was granted for 10 different trusts/foundation trusts in England and 2 local health boards granted approval for the 2 sites in Scotland. The trial sponsor was Glasgow Caledonian University (GCU) and the AMBER trial office was based in the Nursing, Midwifery and Allied Health Professions Research Unit (NMAHP-RU) at GCU. AMBER was registered with the International Standard Randomised Controlled Trial register (ISRCTN 85007023) and on Clinical Trials.Gov (NCT03166007).

Participants

The trial recruited PwMS who reported they were bothered (in their own judgement) by their bowel dysfunction symptoms at 12 sites across UK (n=2 in Scotland and n=10 in England).

Inclusion criteria:

- Bothered by their bowel dysfunction.
- Male or female over the age of 18 years.
- Diagnosis of MS (in a stable phase i.e. no MS relapse for 3 months).
- No major change of medication for 1 month e.g. introduction of disease modifying medications.
- Not used abdominal massage in the previous 2 months.

Exclusion criteria:

- Unable to undertake the massage themselves and did not have a carer willing to do it.
- Unable to understand the trial processes in order to give informed consent.
- Contraindications to abdominal massage, which included the following: history of abdominal/pelvic cancer, hiatus, inguinal or umbilical hernia, rectal prolapse, Inflammatory Bowel Disease, volvulus and pregnancy.
- Abdominal scars, abdominal wounds or skin disorders that may make abdominal massage uncomfortable.

If a potential participant reported recent sudden and severe changes in bowel habits or rectal bleeding, these symptoms were first discussed with the consultant at each site to determine suitability.

Recruitment procedure

The research team at each trial site were responsible for identifying potential participants. Following identification of potentially eligible individuals, a letter of introduction and an 'Expression of Interest Form' was either posted or given to patients at their routine clinic appointment. Each participant approached about the trial was allocated a unique participant identifier number. This consisted of six characters: three letters which were an abbreviation of the site name followed by three numbers which were allocated on a consecutive basis: for example, 001 for first participant. This unique identifier was used throughout the trial and was added to all participant paperwork. Once a completed 'Expression of Interest Form' was returned, a member of the research team telephoned the individual to provide further information and assess eligibility. If they were eligible and willing to take part, participants were sent a baseline appointment letter along with a 7-day bowel diary for completion. The participant completed the bowel diary the week prior to the baseline appointment. Participants were also asked to bring someone who was willing to do the massage to this appointment if required.

Informed consent

Informed, written consent was obtained for all participants at the baseline appointment and included consent to any site specific tests. Ethics agreed to the completion of bowel diaries before the baseline appointment as the participants' consent was implied by them willingly completing the diary. There was no use of this data until participants had provided written informed consent and this method aided recruitment to the trial since it meant there was only one clinic visit required. Participants were made aware that the treatment was allocated at random regardless of any personal preference they had. They had the right to withdraw from the trial at any time and for any reason; all participants were also made aware that withdrawal would not affect their routine care.

The consent form also had the option for the participant to be contacted if they were interested in taking part in the process evaluation interviews. Chapter 5 explains the consent method followed for this part of the study. The GPs of all those who took part in the trial were informed of their involvement.

Randomisation, concealment and blinding

Patients who provided written informed consent were randomly allocated to one of two treatment groups during their baseline appointment: advice to optimise bowel care (Control Group) or advice to optimise bowel care and abdominal massage (Intervention Group). The web-based randomisation service was provided by the Tayside Clinical Trials Unit, a UK Clinical Research Collaboration (UK-CRC) registered trials unit, and research staff at sites carried out the randomisation. In a few instances, the AMBER central office would assist with the randomisation remotely. This took place when there may have been issues for the staff connecting to the web-based randomisation system (room allocation with no computer or web connectivity issues). Group allocation was relayed by telephone to site and copies of the relevant randomisation paperwork sent to all of those involved. Due to the nature of the intervention, it was not possible to blind the participants or site staff to the allocation. Participant group allocation was unknown to the data analysis team. Randomisation was stratified by site and minimised on level of disability (walking unaided, aided or wheelchair bound).

Treatment Group Allocation

Both trial Groups

Participants in both the Intervention and Control Groups received a 6-week intervention consisting of one 'face to face' consultation (baseline appointment) followed by weekly telephone calls to review adherence and any changes/difficulties with their bowel management. This meant that both groups had the same amount of health professional contact. Both groups received 'advice to optimise bowel care' as described below.

Control Group (advice to optimise bowel care)

During the baseline appointment, the participants' existing routine bowel care was reviewed and discussed with them by a member of the site research team. Dietary and fluid advice was provided, participants were encouraged to be more active and use a correct defaecation position which was described to them. Participants were given a copy of the 'Bowel Care Advice Leaflet' of the MS Society which reinforced this advice (https://www.journalslibrary.nihr.ac.uk/programmes/hta/1212712/#/.) (Stand alone Document 1)

Intervention Group (abdominal massage & advice to optimise bowel care)

In addition to optimised bowel care as described for the Control Group, staff delivering the intervention (local health care professionals all fully trained in the massage technique) taught the participant and/or his or her carer how to deliver the abdominal massage. This teaching included:

1) viewing a short trial specific DVD which demonstrated the massage techniques by carer and self-massage (Figure 1 shows a picture captured from the training DVD).
2) provision of a study-specific abdominal massage training booklet.
3) a demonstration of the massage technique on the participant.
4) practice of the various strokes by the carer or participant.

5) an opportunity for the participant and carer to ask questions. Possible adaptations to accommodate a participant's disability were also discussed. A daily massage of 10 minutes duration was recommended.

Figure 1: A picture from the AMBER training DVD which demonstrates the massage strokes being demonstrated.

Participants in this group were given an information pack which consisted of:

- The Multiple Sclerosis Society's Bowel Care Advice booklet.
- The massage DVD.
- Patient abdominal massage training information leaflets.

In order to standardise the intervention delivery across all sites, training for all site staff delivering the intervention was provided by one individual with clinical expertise in the area. Staff attended a trial training day and/or they were trained during the site initiation visits. Each staff member had to perform practical demonstrations and be deemed proficient in the technique before being signed off as fully competent. Sites were contacted after the baseline appointment of their first intervention participant to discuss how staff found delivering the massage and to answer any questions. Further training was available at this point, but all sites felt confident in the delivery of the intervention. Any questions/feedback from the individual sites were shared with all research site staff via monthly update teleconferences. The weekly telephone calls to participants were either done by the staff member who delivered the massage training or another member of staff on the delegation log.

Participants randomised to the Control Group were informed that they would be given access to the massage training materials at the end of their follow up (Week 24). In addition, some

of the sites offered to hold training sessions with the control patients after they had completed the study.

A description of how to perform the massage technique can be found in Appendix 1, along with all the training material given to participants as an aide memoire.

Mechanistic evaluation

One of the sites in AMBER (University College London Hospital) is a regional bowel dysfunction centre where standard anorectal physiology and colonic transit tests are routinely undertaken. AMBER participants recruited at this site underwent the following tests before the intervention and then again at 24 weeks:

- Anorectal Pressure tests: this test involved the insertion of a small probe into the rectum to measure the strength of the anal muscles.
- Anal and rectal sensation and capacity was measured by using a tiny amount of current and inflating a small balloon within the rectum (a balloon was inserted via a tube and sensory thresholds to progressive distension established. The initial tube was then removed and a different catheter with a bipolar electrode inserted: the sensory threshold to milliamp current was then determined.
- Transit tests: 3 sets of radio opaque capsules were posted to the participant who ingested them in the order specified in the instructions on three consecutive days. Participants then attended for abdominal x-ray 2 days after the last capsule to determine total colonic transit time (not segmental transit).

This was a small sub-study in AMBER to look at possible mechanisms involved in bowel dysfunction in PwMS and to look at the feasibility of undertaking such tests within this population and their compliance with attending for the repeat tests.

Data collection and management

Data were collected and recorded on study-specific paper-based Case Report Forms (CRFs) either by site staff or the participants (bowel diaries and patient reported outcomes during weeks 1-6 and week 24). Sites were trained on completion of all the paperwork before

recruitment commenced and monthly teleconferences jointly with all sites allowed any data issues/inconsistencies to be discussed and resolved. The AMBER central office entered all data into the database known as 'OpenClinica' (https://www.openclinica.com). This was set up and managed by Tayside Clinical Trials Unit. A range of data validation checks were used to minimise erroneous and missing data.

Baseline Assessment

Demographic data and information on participants' MS, medical history and bowel symptoms were collected at the baseline assessment. Participants also completed a Questionnaire booklet which contained 5 different questionnaires (including the primary and secondary outcome measures - see the outcome measures section and Appendices 3 and 4). Information on current medication was recorded, including any laxative use. Participants were given all bowel diaries and questionnaires to be completed during the 6 week intervention phase at this appointment with an instruction sheet detailing how they should be completed. Baseline ano-rectal physiology and colonic transit time data were collected on the London participants using an Ano Rectal Physiology case report form.
Baseline assessments were conducted between 22nd Jan 2015 and 19th July 2016.

Participant Follow-up

The duration of follow-up was 24 weeks from date of randomisation.

Outcomes were collected via the following participant-completed documents (see Appendix 2 and https://www.journalslibrary.nihr.ac.uk/programmes/hta/1212712/#/ Stand alone Document 2) :

- A questionnaire booklet at Week 6 and 24 (as per baseline questionnaire).
- A 7-day bowel diary (Control Group) or bowel and massage diary (Intervention Group) at weeks 1-6 and during Week 23.
- Patient Resource questionnaires at weeks 1 to 6, and at 12, 18 and 24.

All information completed by the participants was returned to the AMBER trial central office via reply paid envelopes provided.

Ano-rectal physiology and colonic transit time data were collected at Week 24 in UCL participants only (same measurements as baseline).

Site research staff telephoned all participants weekly during weeks 1 to 6 and again at Week 24 and collected additional information on any potential issues, changes in diet/exercise/fluid, adverse events and any changes in medication. Any potential issues with bowel management or the massage were discussed and fed back to the AMBER central office if deemed necessary.

All AMBER follow-ups were completed by 19th January 2017.

Table 1 shows the AMBER trial matrix and data collected at each time point.

Table 1 AMBER Trial Matrix

Item/time point	Screen	week -1	Baseline Appointment	Call wk 1	Call wk 2	Call wk 3	Call wk 4	Call wk 5	Call wk 6	Posted wk 12	Posted wk 18	Posted and call wk 24	Withdrawal Data collection
Informed Consent			X										
Inclusion/Exclusion	X												
Medical History			X										
Current medications			X	X	X	X	X	X	X			X	X
Randomisation			X										
7-day bowel diary		X	X	X	X	X	X	X	X			X	X
Process evaluation/interviews [a]							X					X	
7-day bowel and massage diary [a]			X	X	X	X	X	X	X			X	X
Trial Questionnaires [c]			X						X			X	X
Physiology Forms [b]			X						X			Visit	X
Patient Resource Questionnaire				X	X	X	X	X	X	X	X	X	
Adverse Events				X	X	X	X	X	X			X	X

(a) Only participants in Intervention Group (b) Only participants in London sub study (c) Trial Questionnaires include Neurogenic Bowel Dysfunction Score, SF Qualiveen, EQ-5D-5L, constipation scoring system and the NBD-PROM Questionnaire wk - Week

Outcome Measures (Stand alone Document 2 (https://www.journalslibrary.nihr.ac.uk/programmes/hta/1212712/#/)

Primary Outcome: Neurogenic Bowel Dysfunction Score (NBDS)

The NBDS[32] is a 10 item questionnaire covering frequency of bowel movements (0-6 points), headache, perspiration or discomfort during defaecation (0-2 points); medication for constipation or faecal incontinence (0-4 points each); time spent on defaecation (0-7 points); frequency of digital stimulation or evacuation (0-6 points); frequency of faecal incontinence (0-13 points); flatus (0-2 points); and perianal skin problems (0-3 points). The maximum score is 47; the higher the score, the more severe the symptoms, with a score of 14 or more rated as severe. In the AMBER trial, the primary outcome measure was the change in the NBDS from baseline to Week 24.

Secondary outcomes

Bowel Symptoms

The Constipation Scoring System (CSS) [33] was completed at baseline, 6 and 24 weeks to assess constipation symptoms. The CSS is an 8-item questionnaire with items on frequency of bowel movement, difficulty with evacuation, feeling of incomplete evacuation, pain, length of time for evacuation, assistance with evacuation, number of failed attempts and the duration of constipation. Maximum score is 30, with higher scores indicating greater severity. A 7-day bowel diary (designed for use in the AMBER study) was used to record information on bowel symptoms such as frequency of bowel movement, time spent defaecating, stool type (Bristol stool chart) (Appendix 3), laxative use, additional interventions, e.g. digital stimulation and if there were any episodes of bowel incontinence. The diary was completed prior to baseline, during weeks 1–6 and at week 23. In the Intervention Group, a 7-day massage diary was used to record daily information on massage compliance and duration and was completed prior to baseline, during weeks 1–6 and at Week 23.

Bladder Dysfunction

Bladder function was measured using the Qualiveen Questionnaire Short Form consisting of an 8-item questionnaire assessing bladder dysfunction, such as leakage and signs of incomplete voiding [34]. Often, if patients with MS are suffering from constipation, they report that their bladder symptoms are worse, especially urgency and frequency, which can lead to an increase in urinary incontinence. This outcome measure allowed the effect of the change in bowel function on the bladder to be assessed at baseline, Week 6 and 24. A higher score indicates a poorer quality of life.

Quality of life outcomes

A. For health status the EuroQol five-dimension questionnaire (EQ-5D-5L) generic questionnaire was used.[35] Participants completed the EQ-5D 5L at baseline, Week 6 and 24.

B. A Neurogenic Bowel Dysfunction patient-reported symptom and quality of life questionnaire (NBD-PROM) was completed at baseline, at 6 and 24 weeks. This score was developed by one of the collaborators on the AMBER trial as part of a National Institute for Health Research (NIHR)-funded postdoctoral fellowship. The questionnaire has three subscores: quality of life, faecal incontinence and symptoms and includes four stand-alone items. It is intended for use with individuals with a range of conditions which result in neurogenic bowel dysfunction. The measure's reliability and criterion validity will be evaluated.

Economic outcomes

The cost and use of NHS services was collected via a 'Patient resource questionnaire' (https://www.journalslibrary.nihr.ac.uk/programmes/hta/1212712/#/) (Stand alone document 2) during weeks 1-6 and at weeks 12, 18 and 24. From this information (along with the EQ-5D-5L data) the costs and quality adjusted life years (QALYs) were calculated for each group. A cost utility analysis was conducted to calculate the incremental cost per QALY of abdominal massage compared to optimised bowel care and this is described in

detail in Chapter 4.

Change of medication

Changes of medication were recorded using a current medication form. Any changes to the participant's medications during their involvement in the trial were recorded. Also recorded were any reductions or stoppage of laxatives between baseline and Week 24.

Radio Opaque marker transit tests

Different parameters were collected on an ano-rectal CRF (Supplementary Mateial) for the physiology and transit tests. The total number of markers remaining in the gut at abdominal x-ray was analysed to determine any differences between baseline and Week 24 and all other data were summarised.

Adverse events

Expected events arising from the treatments in AMBER are noted below and are common in individuals with constipation and thus were not collected as Adverse Events (AEs) but noted in the weekly follow-up data collection:

- Increased flatulence
- Abdominal cramps
- Stomach rumblings/noises
- Loose stool, which in some instances may lead to faecal incontinence.

All AEs (where a participant sought healthcare professional intervention) and serious AEs (including the following: death; life threatening conditions; in-patient hospitalisation or prolongation of existing hospitalisation; persistent or significant disability or incapacity) were assessed for causality, severity and expectedness and were reported to the relevant regulatory bodies. If a site was in doubt as to whether an event was an AE, this was reported and discussed prior to data lock. Any AEs which were deemed as ongoing at the end of the trial were reviewed and further clarification from the site was sought. If the AE was still ongoing after this (due to the nature of the event, but not related to the intervention), this was where the follow up ended.

AEs (including serious adverse events) were coded with MedDRA 16.1 and reported by primary System Organ Class (SOC) and Preferred Term (PT). Participants were counted only once when calculating the incidence of AEs. An overview table was created counting the number of AEs by SOC and PT.

Sample Size

The sample size for the RCT was based on the NBD score using data from a pilot study[36] which provided the only published data available on abdominal massage in this group of patients. That study found a difference of 4.21 points on the NBD between those receiving the intervention (mean score at eight weeks of 6.86; standard deviation of 3.8) and the comparison group (mean score at eight weeks of 11.07; standard deviation of 7.02). Other outcomes in that study changed in favour of the intervention and participants anecdotally reported that the massage was relaxing and were keen to do it themselves. Using these data we selected a minimum clinically important difference (MCID) of 4.21 and selected the higher standard deviation of 7.02 seen in the comparison group as the basis for our sample size calculation.

Using these data, sixty per group was calculated as necessary to detect a difference between groups of 4.21 (standard deviation, SD 7.02) at a 5% level of significance with 90% power. Thus, for a fully powered study, the total sample size, allowing for a 20% drop-out, was 150. However, in response to suggestions from the funding body, the sample size was increased to 200 (100 per group), which allowed for greater attrition.

Statistical analyses

Statistical Methods for analysis of the main primary and secondary outcomes are detailed below and also in the statistical analysis plan (Appendix 5). This document was drawn up by the trial statisticians and reviewed by the Project Management Group and was formally signed off by the Chief Investigator and Trial Statistician before analysis commenced.

Analysis Populations

Analysis was performed for the intention-to-treat population and is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT).[37]

Subgroups

Subgroup analyses were carried out by first testing for a subgroup factor by intervention interaction. If this was significant at the 5% level, results were estimated separately by the different subgroups. This included a secondary analysis comparing those who undertook the massage themselves compared to carer massage.

Missing Data

The extent of missing data was explored in the outcomes especially the primary outcome. Patterns of missing data were explored and predictors of missingness examined, especially if these vary by intervention. A table was constructed to assess differences in characteristics of those with complete data and those with missing data for the primary analysis. Multiple imputation was implemented for the primary outcome, assuming data were missing at random (MAR).

Summary of Trial Data

All continuous variables were summarised using the following descriptive statistics: n (non-missing sample size), number of missing records, mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels was reported for all categorical measures. In general, all data were listed, sorted by subject and treatment and where appropriate by visit number within subject.

All summary tables were structured with a column for each treatment in the order (Intervention, Control) and an additional column for the total population relevant to that table/treatment, including any missing observations.

Demographic and Baseline Variables

Baseline characteristics for patients are: age, gender, BMI, type of MS, site, disease duration (years since diagnosis), cognitive symptoms of MS and level of mobility (walking unaided, aided or wheelchair bound).

Prior and Current Medications

Prior medications were all medications which are currently taken by the patient but commenced prior to trial start. Concomitant medications are all medications commenced during the trial, and all changes to the dosing of prior medications. Prior medications were listed but not analysed. Concomitant Medications were analysed by number of medications taken.

Treatment Adherence

Treatment adherence was calculated from the weekly bowel diaries. The number of times the bowel massage was done per week was used in the main analysis. For the Control Group, this number was set to 0.

Efficacy Analyses

Data for continuous outcome measures (both primary and secondary) were assessed for normality prior to analysis. Transformations of the outcome variables were used where necessary if these were not normally distributed.

If data were normally distributed, outcome measures were assessed by multiple linear mixed model regression. The primary analysis consisted of comparisons between treatment groups (bowel massage versus no massage) at the final visit (Week 2424), adjusted for site, minimisation variable level of mobility (walking unaided, aided or wheelchair bound) as well as baseline measure of the outcome, and gender.

In a secondary analysis of the primary outcome, additional baseline variables age, gender, BMI, type of MS, site disease duration (years since diagnosis) and cognitive symptoms of MS were included in the model.

Where data were not normally distributed and could not be transformed into a normal distribution, data were analysed using non-parametric methods in addition to multiple linear regression.

In addition to the comparison of baseline versus Week 24, a repeated measures mixed model analysis was performed on the outcomes using all available visits.

Data for categorical outcome measures were assessed by logistic regression in the same way as described for continuous outcome measures.

Primary Efficacy Analysis

The primary outcome measure was the between group difference in the change of NBD Score at 24 weeks and analysis adjusted as described above.

Secondary Efficacy Analyses

Bowel Outcomes

- Between group difference in change in constipation symptoms. Analysis variable is the total constipation score.

- Bowel Symptoms (7-day bowel diary). The percentage of normal stools per week was calculated and used for analysis. In addition, number of days when stool was passed and time spent passing stool was analysed.
- Radio Opaque marker transit tests. The number of total markers was used for the analysis.
- Adherence to massage schedule (massage diary). As this is only available for the treatment group, data are summarized in the descriptive statistics. No formal testing was done.

Urinary Outcomes

- Between group difference in change in total score of bladder function (Qualiveen Questionnaire Short Form).

Quality of Life Outcomes

- Between group difference in change in health-related quality of life measured by EQ-5D-5L questionnaire using both the EQ-5D VAS and index score.
- Between group difference in change of Patient reported Quality of life. This consists of 4 scores derived from the NBD patient reported outcomes tool.
- Between group difference in change in medication, analysed as all patients who stopped using laxatives at Week 24. This was determined from the concomitant medication page.
- Between group difference in change in medication, analysed as the number of changes in usual laxative use at Week 24. This was taken from the bowel diary as the number of changes from usual laxative use to less laxative use at Week 24.
- Between group changes in the regular use of medications against constipation was assessed for changes at Week 6 and 24.

Reporting Conventions

P-values ≥0.001 are reported to 3 decimal places; p-values less than 0.001 are reported as '<0.001.' The mean, standard deviation, and any other statistics other than quantiles, are reported to one decimal place greater than the original data. Quantiles, such as median, or

minimum and maximum, use the same number of decimal places as the original data. Estimated parameters not on the same scale as raw observations (e.g. regression coefficients) are reported to 3 significant figures.

All analysis was performed using SAS 9.3. All data, analysis programmes and output was kept on the Mackenzie Server and backed up according to the internal TCTU IT Standard Operating Procedures.

Analysis programs were required to run without errors or warnings. The analysis programmes for outcomes were reviewed by a second statistician and any irregularities within the programmes were investigated and fixed and date of finalised analysis programmes were signed and recorded.

Economic analysis

The cost of abdominal massage and optimal bowel care relative to optimised bowel care alone in PwMS who have NBD was considered from NHS and patient perspectives. Healthcare resource use by patients in both trial Groups was collected at each of the follow-up time periods (weeks 1–6, 12, 18 and 24). This included contact with health professionals and medications prescribed. These were costed using NHS pay and prices or, where appropriate, using other (e.g. market-based) sources. Economic analysis (including the methods used) is detailed in Chapter 4.

Important changes to protocol after trial commencement

All sites used Protocol Version 2, dated 18th November 2014 throughout the trial duration. The London site used an additional Patient Information Leaflet (PIL) to describe the additional tests carried out at this site. After original approval of the PIL, one of the tests was no longer completed routinely at the London site so this information was removed and the amended PIL was approved by all relevant regulatory bodies. This change was carried out before any patients were recruited at the site.

Another substantial amendment was to incorporate a sub-study, entitled SWAT 24 within AMBER. Participants were randomised to receive either the original cover letter or an

enhanced cover letter (sent with the 24 week questionnaire) to evaluate whether the wording used would increase return rates of the questionnaires.

Data from the sub-trial will contribute to Trial Forge initiative to improve trial efficiency (http://www.trialsjournal.com/content/16/1/261)

and to the Cochrane review of strategies to improve trial retention (http://onlinelibrary.wiley.com/doi/10.1002/14651858.MR000032.pub2/abstract).

It will help to increase the evidence base on the retention of participants to trials. The only change to AMBER was the way the cover letter sent with questionnaires was written (no protocol change).

Other non–substantial changes included:

- Addition of new sites as the trial progressed (original target was 10 sites but final total was 12 sites).
- Set-up of 2 Patient Identifying Centres (PICs) to assist 2 sites with their recruitment.
- Sites collecting the NBD score during the 24-week telephone call with participants to maximise the primary outcome data in the study.

Trial Oversight

The trial was led by the Chief Investigator who, along with the Trial Management team members (consisting of a trial manager, a data coordinator and a process evaluation researcher), were employed by the Nursing, Midwifery and Allied Health Professions Research Unit (NMAHP RU).

The trial was overseen by a Project Management Group (PMG), a Trial Steering Committee (TSC) and a Data Monitoring Committee (DMC).

The PMG had a teleconference approximately every 4-6 weeks during the recruitment period and then bi-monthly after this. The group's role was to support any decision making that the Trial Management team needed further advice on.

The TSC had both an independent chairperson and members but also consisted of the trial collaborators. The TSC had 4 meetings over the course of the trial with additional updates on recruitment when requested. The TSC commended the team on recruiting to target and on time.

An independent DMC, chaired by a statistician, had 3 meetings over the course of the study, and additional updates were provided when requested. All statistical reports to the DMC were prepared by a statistician from the Tayside Clinical Trials Unit. The DMC had no issues with the trial continuing at any time-point and commended the team on the recruitment and management of the study. The DMC charter can be reviewed in Appendix 3.

Patient and Public Involvement

The AMBER study has had active participation with a group of people with MS (here on in called the MS focus group). Some of the group were involved with the development of the grant application providing feedback on the lay summary, trial design and appropriate outcome measures and questionnaires. Several additional people with MS became involved during the very early stages of the trial and throughout implementation and dissemination of results. The group included males and females, with various levels of disability and ages and some with and without bowel dysfunction. Approximately 10 members of the group attended each of the meetings. Material to review was sent electronically prior to the meetings, was available in hard copy at the meetings and very helpful feedback and discussions took place. One of the members of the focus group has also attended each TSC meeting as a lay representative and has actively engaged in the conversations and discussions at each meeting. Prior to recruiting any participants the MS focus group reviewed the massage training DVD and the massage training material which would be given to the participant to take home with them and their input to this was extremely influential. The group's opinion of the initial version of the training DVD was that the visual was excellent but the language used was "too clinical". This was overcome by the CI of the study doing a voice over on the DVD and the group reviewed this again and it was deemed much more acceptable and user friendly. Many of the trial participants subsequently commented that they thought the video was extremely useful and easy to follow.

We also initially had 2 different training documents and we asked the group which would be better used as an Aide memoire. The MS focus group had very mixed opinions on their preferences with discussions had on style, language and diagrams used. It was therefore concluded that both of these additional training materials would be provided to all participants in the intervention arm and they could decide which material they felt was better for them. However, there is the possibility of combining the information into one single training document if the intervention is rolled out to clinical care.

Participants in AMBER were given quite a lot of information at the baseline appointment to take way with them, in the form of a "follow up pack". This pack included all the questionnaires and bowel diaries, study instructions on what they had to complete over the 6 week intervention period and also the massage training DVD and reading materials (only if the participant was on the intervention arm). The MS focus group reviewed this pack and thought it was logical and clear and some further feedback from site staff implied that the participants "liked" having this pack to take away with them.

We have kept in touch with the MS focus group throughout the study, giving updates on recruitment and there were discussions on dissemination plans. It is hoped to have at least two dissemination workshops in the autumn of 2017 for all the research staff involved in the study with possibly extending invites to participants and the MS focus group will be actively involved in some of the material for these events.
Throughout the active recruitment of the study local and national MS charities were aware of our research and promoted the study where regulations allowed.

CHAPTER 3 Results

Trial recruitment

Recruitment overall was considered very successful and Figure 2 shows how well the actual recruitment met the expected monthly targets over the 18 months of active recruitment. The trial oversight committees agreed to stop recruitment on time at 191 participants after reviewing attrition information. Twelve sites recruited participants from 22nd January 2015 to 19th July 2016 and each site recruited between 9 and 26 participants (Appendix 4).

Figure 2. Predicted Recruitment versus Actual recruitment

The CONSORT diagram (figure 3) shows the movement of participants through the AMBER study. In total 237 patients with MS and possible bowel problems were screened, (approximately 61% of the 389 approached by the research staff) and 191 (80% of those screened; 49% of those approached) were randomised. The near 50% uptake on those approached versus those randomised was in accordance with the estimate of uptake stated in the protocol.

Twenty-two of the randomised participants did not complete the study. Two of these were post randomisation exclusions (essentially randomised in error) and data were not collected from these two participants. Thus the analysis was based on 189 participants; 90 in the abdominal massage + advice on optimised bowel care group (Intervention) and 99 in the advice on optimised bowel care group (Control). The inequality in the number of participants per group was due to minimisation at site level.

For the 20 correctly randomised participants (15 intervention, 5 control) who did not complete the study, baseline data were successfully collected and all participants agreed that their existing data could be used. Participants either withdrew (11 in intervention; 3 in control) or were lost to follow up (4 in intervention; 2 in control). In some instances if the data was not returned the Week 6 and 24 follow-up data collection was completed by the researcher during a telephone call. This explains the differing numbers for the NBD score in the CONSORT diagram at Week 6 and 24 in relation to reported withdrawals or lost to follow up.

Appendix 6 gives contextual information, recruitment and retention data for all 12 sites.

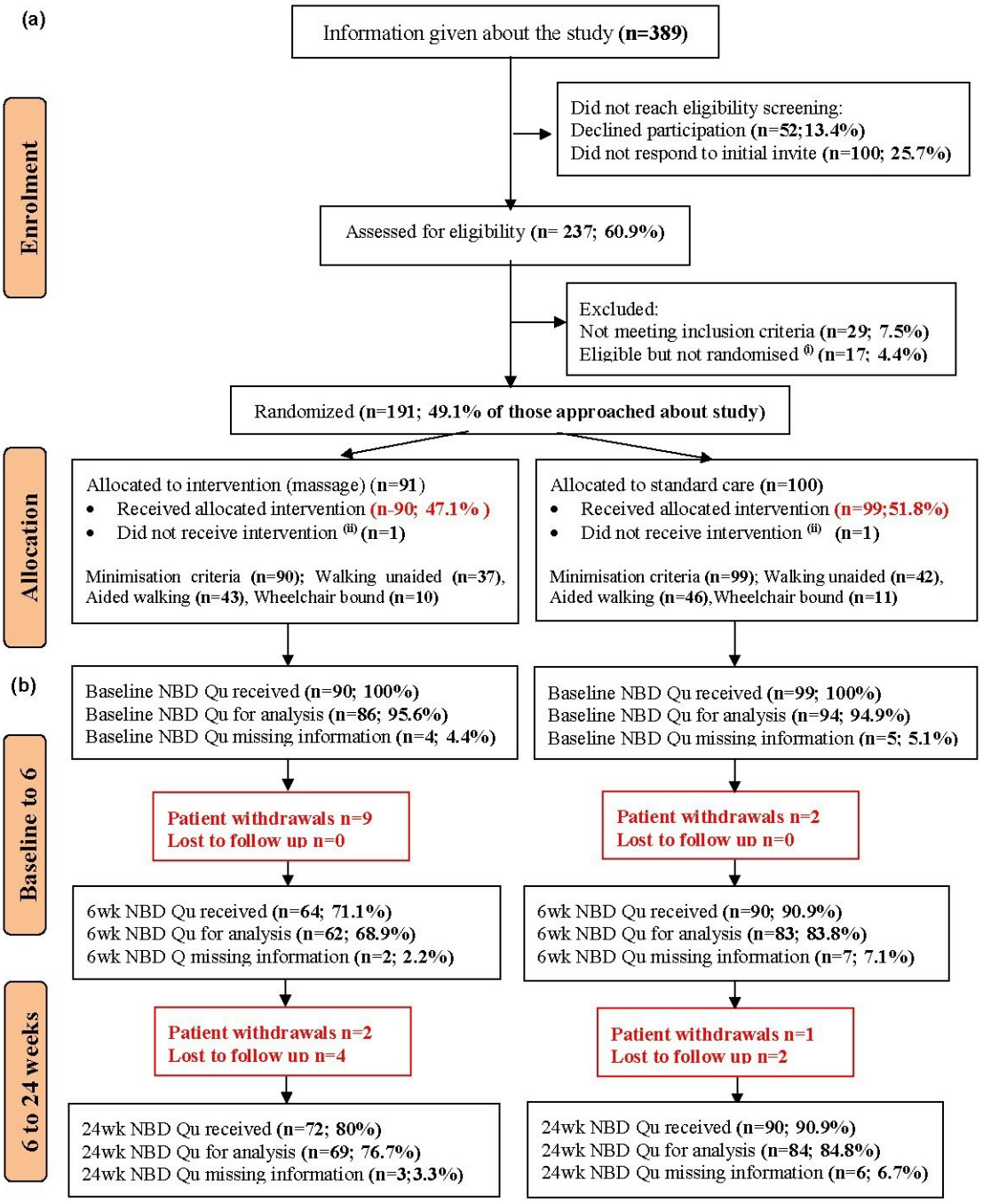

Figure 3. Consort Diagram; Part (a) shows enrolment and screening information; all percentages calculated from those approached about study (n=389). Part (b) shows the breakdown for the primary outcome measure (NBD score) at each stage of data collection; baseline, Weeks 6 and 24; all percentages calculated in part (b) are from n=90 (Intervention Group) and n=99 (Control Group). (i) Reasons for those who were eligible but did not take part vary from the patient's personal circumstances changing to baseline appointments being made for the patient and them not attending. (ii) In each arm, a patient was randomised and subsequently eligibility was reassessed and the patient was deemed no longer eligible for the study. No data were collected for these 2 participants. iii) 'Qu' = questionnaire.

Quality of participant completed outcome data

Participant completed outcomes were returned via post at Weeks 6 and 24. Questionnaire and bowel diary data were checked for completeness and all effort was made to collect any missing information where acceptable to do so.

Figure 3 (the consort diagram) shows the numbers available for the primary outcome analysis at Baseline, Week 6 and 24 (NBD score). During monitoring of the study attrition rates and primary and secondary outcome data received, it was evident that some participants were stating they had returned their outcome measures in the post but these were not received in the AMBER study office. Thus in order to maximise our available primary outcome data for analysis, from 22nd March 2016 onwards the research staff at each site completed the NBD score (10 questions) during the 24-week telephone call. This increased our available data for primary outcome analysis at 24 weeks, compared to 6 weeks, in both study groups (76.7% in Intervention and 84.8% in the Control).

Compared to the Control Group there was a greater number of withdrawals/lost to follow ups in the Intervention Group (15/90 versus 5/99).

For all outcome data, the numbers available for analysis and any reasons for missing data will be reported when discussing each outcome below.

Reasons of withdrawal/loss to follow-up –

There were 2 randomisation failures and 20 participants who withdrew and were lost to follow up (14 in the Intervention Group; 6 in Control Group; none withdrew consent to data already collected). We have undertaken analysis of the missing data (Appendix 5) and it would seem that it does not suggest any major biases in the primary analysis. The reasons for withdrawal in the intervention group were indeed varied and included change in diagnosis of MS, family circumstances, worsening of condition, amount of paperwork too much. There is also the possibility that those in the Control Group remained in the study so they would receive the training in the abdominal massage and had not yet experienced the potential disappointment of the intervention not working for them, which might increase the likelihood of withdrawing from the study. Interestingly, of those who took part in the interview study none withdrew or were lost to follow-up, which may indicate this was a more motivated group or that taking part in the interviews facilitated retention.

Missing Primary Outcome Data

The missingness of the primary outcome data appeared to be relatively unrelated to the baseline characteristics apart from trial group (more in Intervention Group), more in those not wheelchair bound, slightly more in females, slightly more in younger and more in some centres. See Appendix 5; differences in characteristics of missing NBD score at 24 weeks compared to complete data (possible reasons for all of the above will be included in the discussion, Chapter 6). However, using the characteristics at baseline to impute missing data, multiple imputation (MI) was carried out for the primary outcome and the primary analysis repeated as a sensitivity analysis. This approach assumes data is missing at random (MAR) and this is discussed further in Chapter 6.

Baseline data

The mean age of participants was 53 years (SD 10.4) and 81% (154/189) were female. Mean time since diagnosis of multiple sclerosis was 14.3 years (SD 9.1). Baseline demographics and clinical data are summarised in Table 2. Demographics and symptom characteristics of the two groups were similar comparable at baseline.

Table 2 Characteristics of participants at study entry

Characteristic	Intervention Group (N = 90)	Control Group (N = 99)
Clinical characteristics		
Minimisation variable Walking aids – no. (%)		
- Walking unaided	37 (41.1%)	42 (42.4%)
- Aided walking	43 (47.8%)	46 (46.5%)
- Wheelchair bound	10 (11.1%)	11 (11.1%)
Age (years) - mean (SD)	53.5 (11.32)	51.3 (10.32)
Gender – no. (%)		
- Male	14 (15.6%)	21 (21.2%)
- Female	76 (84.4%)	78 (78.8%)
BMI (kg/m2) – mean (SD)	27.4 (6.207)	26.22 (5.525)
Duration of MS (years) – mean (SD)	14.8 (9.76)	13.9 (8.64)
Type of MS – no. (%)		
- Benign	0 (0.0%)	2 (2.0%)
- Relapsing Remitting	45 (50.0%)	61 (61.6%)
- Secondary Progressive	36 (40.0%)	23 (23.2%)
- Primary Progressive	9 (10.0%)	13 (13.1%)
Severity of symptoms – cognitive – no. (%)		
- None	39 (43.3%)	35 (35.4%)
- Moderate	50 (55.5%)	61 (62.6%)
- Severe	1 (1.1%)	3 (3.0%)
Severity of symptoms – pain – no (%)	41 (46.6%)	46 (46.5%)
- None	43 (47.8%)	52 (52.5%)
- Moderate	6 (7.6%)	1 (1.0%)
- Severe		
Severity of symptoms – spasm- no (%)	33 (36.7%)	31 (31.3%)
- None	58 (64.4%)	63 (64.7%)
- Moderate	17 (12.2%)	11 (11.1%)
- Severe		
Severity of symptoms – depression- no (%)	41 (45.6%)	52 (52.5%)
- None	45 (50%)	42 (43.5%)
- Moderate	4 (4.4%)	4 (4%)
- Severe		
Severity of symptoms –fatigue- no (%)	8 (8.9%)	5 (5.1%)
- None	58 (64.5%)	68 (68.7%)
- Moderate	24 (26.7%)	26 (26.3%)
- Severe		
Severity of symptoms – bladder - no (%)	12 (13.3%)	15 (15.2%)
- None	57 (63.4%)	59 (59.6%)
- Moderate	29 (32.2%)	29 (29.3%)
- Severe		

Bowel Symptoms

To be eligible participants had to be 'bothered' by their constipation. Bowel symptoms had commenced more than 10 years ago in 37% and less than one year ago in 4%. The main bowel symptoms reported by participants at baseline were feeling of incomplete emptying, straining to pass stool, and bloating (Table 3).

Table 3: Bowel symptoms reported in case report form

Bowel symptoms	**Intervention Group(N = 90)**	**Control Group (N = 99)**
Pain – Yes	59 (65.6%)	60 (60.6%)
Bloating – Yes	76 (84.4%)	86 (86.9%)
Faecal Incontinence – Yes	39 (43%)	60 (60.6%)
Successfully opening of bowels 2-4 times a week	59 (65.6)%	53 (53.5%)
Type of stool (Bristol Stool chart) Over the last week **Types 1 & 2** **Types 3 & 4** **Types 5, 6 & 7** **No stool** **Missing** **Constipated (No stool+ Type 1&2)**	 21.8% **20.2%** 16.1% 39.8% 2.3% **61.6%**	 19.4% **23.6%** 14.6% 38.8% 2.4% **58.2%**
Straining to pass stool - Yes at least 25% of the time	80(88.9%)	74(74.8%)
Digital Stimulation - Yes at least 25% of the time	28(31.1%)	29(29.3%)
Feeling of incomplete emptying - Yes at least 25% of the time	83(92.8%)	94(94.9%)

Table 4. Summary of Primary and Secondary Outcomes at Baseline, Week 6 and Week 24

		Intervention Group (n = 90)			Control Group (n = 99)		
Score	**Time**	**Mean (SD)**	**n**	**Median (Range)**	**Mean (SD)**	**n**	**Median (Range)**
Primary Outcome Measure– Symptom severity							
NBD[1]	**Baseline**	7.6 (5.3)	86	6 (0 – 21)	8.6 (5.1)	94	9 (0 – 22)
	Week 6	8.4 (6.2)	62	7 (0 – 25)	9.1 (5.7)	83	8 (0 – 34)
	Week 24	7.4 (5.2)	69	7 (0 – 24)	8.7 (5.7)	84	7.5 (0 – 24)
Secondary Outcome Measure – Symptom severity							
Constipation Score[2]	**Baseline**	11.7 (4.1)	88	12 (1 – 25)	11.5 (3.8)	97	11 (3 – 21)
	Week 6	10.6 (4.3)	58	11 (1 – 22)	10.8 (4.0)	83	11 (1 – 22)
	Week 24	10.1 (4.1)	57	10 (2 – 22)	11.1 (3.9)	81	11 (3 – 27)
Bowel Diary Data							
Time spent on toilet (minutes /week)	**Baseline**	75.6 (69.6)	80	57.5 (3 – 330)	75.8 (74.4)	87	55.0 (3 – 370)
	Week 6	77.9 (73.3)	66	55.0 (5 – 315)	85.0 (88.5)	85	50.0 (2 – 400)
	Week 24	78.2 (92.4)	53	45.0 (3 – 550)	77.0 (68.5)	78	56.5 (1 – 295)
Bowel Diary Data							
Attempts to empty the bowels / week	**Baseline**	10.4 (6.7)	86	9 (0 – 35)	8.6 (5.2)	91	8 (0 – 32)
	Week 6	11.3 (7.1)	65	9 (2 – 32)	8.9 (6.0)	88	8 (1 – 32)
	Week 24	10.7 (7.2)	53	10 (1 – 43)	8.3 (5.1)	77	7 (1 – 23)
Bowel Diary Data							
Stools passed per week	**Baseline**	3.9 (1.7)	88	4.0 (0 – 7)	4.0 (1.7)	98	4 (0 – 7)
	Week 6	4.3 (1.9)	68	4.5 (1 – 7)	3.9 (1.8)	89	3 (0 – 7)
	Week 24	4.3 (1.9)	57	4.0 (0 – 7)	3.9 (1.9)	81	4 (0 – 7)
Bladder symptom severity							
Qualiveen Total Bladder Score[3]	**Baseline**	1.8 (1.10)	90	1.8 (0-4)	2.0 (1.20)	99	1.8 (0-4)
	Week 6	1.7 (1.13)	61	1.6 (0-4)	2.1(1.15)	85	2.1(0-4)
	Week 24	1.7 (1.10)	57	1.8 (0-4)	2.1(1.12)	81	2.0 (0-4)

Quality of Life							
EQ-5D-5L Visual Analogue Score[4] Max 100	**Baseline**	60.6 (21.1)	89	60 (3 – 100)	55.7 (20.6)	98	60 (3 – 100)
	Week 6	59.4 (24.0)	59	65 (5 – 97)	55.4 (20.8)	86	60 (5 – 100)
	Week 24	59.8 (22.6)	58	62.5 (10 – 95)	51.3 (20.3)	83	50 (10 – 90)
EQ-5D-5L Health Index Score[5]. Maximum score 1	**Baseline**	0.50 (0.25)	95	0.6 (-0 – 1)	0.50 (0.28)	99	0.6 (-0 – 1)
	Week 6	0.50 (0.29)	60	0.6 (-0 – 1)	0.50 (0.27)	84	0.5 (-0 – 1)
	Week 24	0.50 (0.28)	58	0.6 (-0 – 1)	0.50 (0.28)	83	0.5 (-0 – 1)
New quality of life measure for validation (NBD PROM)							
NDB PROM[6] Total Score Maximum 52	**Baseline**	20.2 (8.5)	86	20 (6 – 41)	20.8 (7.4)	98	21 (5 – 38)
	Week 6	19.9 (8.2)	56	19 (5 – 42)	21.4 (7.0)	82	21 (3 – 42)
	Week 24	19.0 (8.4)	56	18 (5 – 50)	20.9 (7.4)	77	21 (1 – 40)
NBD PROM QOL Maximum 24	**Baseline**	9.6 (5.1)	88	9 (0 – 22)	10.7 (4.7)	99	11 (1 – 22)
	Week 6	9.9 (4.9)	56	10 (0 – 21)	10.7 (4.3)	83	11 (1 – 23)
	Week 24	9.2 (4.8)	58	8.5 (2 – 23)	10.7 (4.7)	80	11 (0 – 24)
NBD PROM Faecal Incontinence Score Maximum 12	**Baseline**	3.7 (2.4)	90	3 (0 – 10)	3.7 (2.0)	99	3 (0 – 9)
	Week 6	3.6 (2.3)	61	3 (0 – 9)	4.1 (2.1)	87	4 (0 – 11)
	Week 24	3.8 (2.5)	57	4 (0 – 12)	4.1 (1.8)	82	4 (0 – 9)
NBD PROM Symptom Score Maximum 16	**Baseline**	6.9 (2.9)	88	7 (0 – 16)	6.4 (3.1)	98	6 (1 – 13)
	Week 6	6.4 (3.2)	60	6 (1 – 14)	6.6 (2.5)	84	6 (1 -14)
	Week 24	6.0 (2.8)	57	6 (1 – 15)	6.2 (2.8)	80	6 (0 - 14)

(1) NBD 0-47, ≥14 severe; (2) Constipation Symptom Score 0-30, 30 severe; (3) Qualiveen Total Bladder Score 0-4, higher score worse; (4) EQ-5D-5L Visual Analogue Score Max 100 Higher is better quality of life; (5) EQ-5D-5L Health Index Score Maximum score 1 indicates best health; (6) NBD PROM higher scores for all indicates greater improvement.

Primary Analyses

The primary analysis is the comparison between treatment groups (bowel massage versus no massage) at the final visit (24 weeks), adjusted for site, minimisation variable level of mobility (walking unaided, aided or wheelchair bound) as well as baseline measure of the outcome, and gender.

Primary Outcome Measure

Neurogenic Bowel Dysfunction Score (NBDS)

At baseline the mean score for the Intervention Group was 7.6 (SD 5.31), median 6.0 (range 0-21), and in the Control Group 8.6 (SD 5.08), median 9.0 (range 0-22) (Table 4). These scores indicate that the bowel dysfunction symptoms were having a minor impact on the majority of participants (scores of 7-11 indicate minor impact). Scores of 14 or more indicate severe impact. The scores at Week 24 were 7.4 (SD 5.23), median 7.0 (range 0-24) for the Intervention Group and 8.7 (SD 5.70), median 7.5 (range 0-24) for the Control Group. The mean adjusted difference in change between randomised groups from Baseline to week 24 was not statistically significantly different (mean difference between groups Intervention- Control -1.6,4 95% CI -3.32, 0.04, p=0.0558; Table 5). Figures 4 and 5 visually show the change over time within the two groups.

Table 5. Analysis of change from baseline of the Neurogenic Bowel Dysfunction score

	Intervention Group (N=90)		Control Group		Mean difference in change between groups [Intervention-Control], mixed models	
Change from Baseline	N	Mean Change (95% CI)	N	Mean Change (95% CI)	Adjusted* (95% CI)	p-value
Change in Neurogenic Bowel Dysfunction Score						
Baseline to Week 6	61	0.6 (-0.73, 1.98)	80	0.9 (-0.5, 2.22)	-0.58 (-2.38, 1.22)	0.5236
Baseline to Week 24	66	-0.6 (-2.11, 0.93)	80	0.5 (-0.78, 1.83)	-1.64 (-3.32, 0.04)	0.0558

* Adjusted for Baseline value, Centre, Mobility (Walking unaided, Aided walking, wheelchair bound) and Sex. Centre was entered as a random factor.

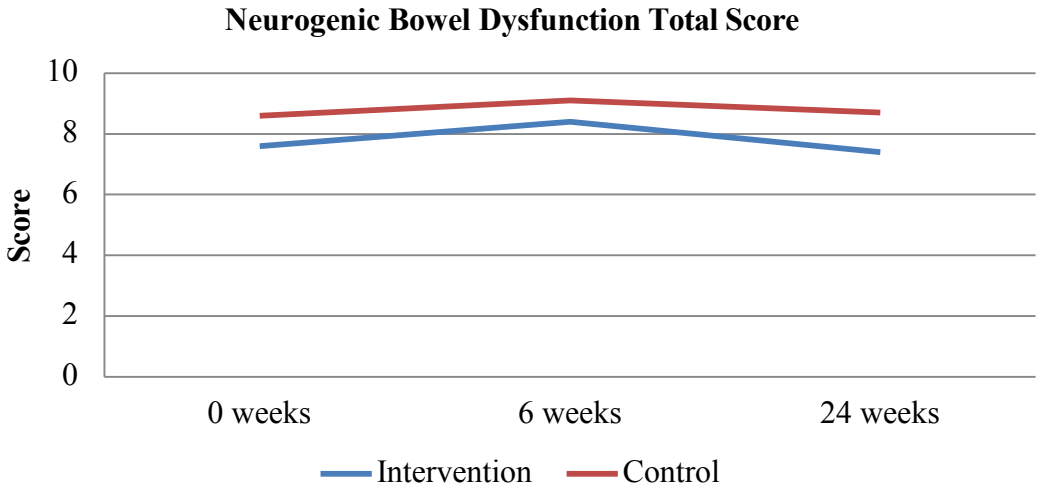

Figure 4. Change in NBD score over time

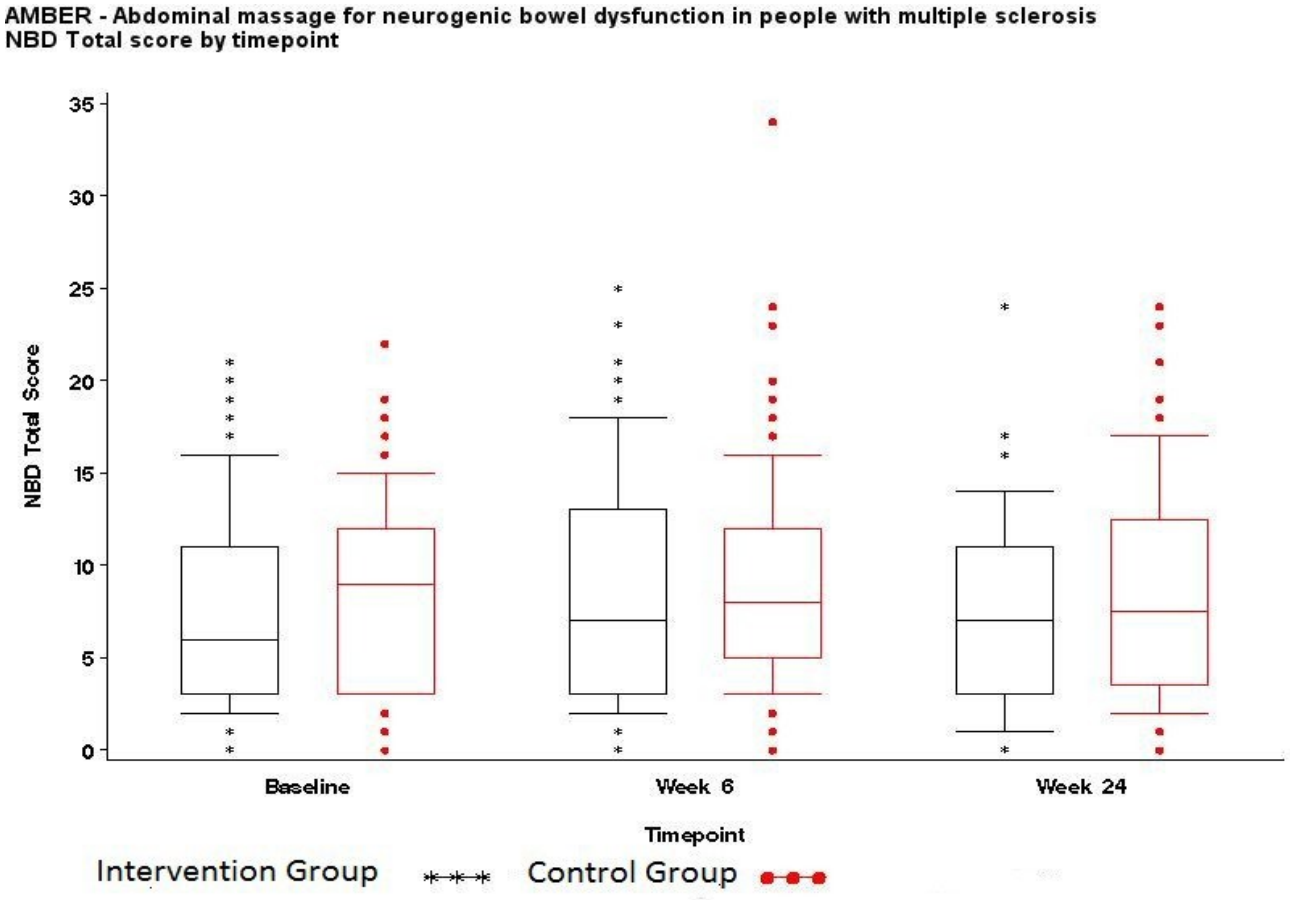

Figure 5. Box and whisker plot for Neurogenic Bowel Dysfunction Score

Secondary Outcomes

Constipation Scoring System (CSS)

At baseline the Intervention Group had a mean CSS score of 11.7 (SD 4.05), and the Control Group had a mean CSS score of 11.5 (SD 3.77). At Week 24 the Intervention Group had a mean score of 10.1 (SD 4.10), and Control Group mean 11.1 (SD 3.91). Figure 6 is a line graph showing the change over time in the two groups. There was no significant mean difference between groups in change in the total CSS Score between baseline and either time-point (Table 6).

Table 6. Analysis of change from baseline in the Constipation Scoring System

	Intervention group (N=90)		Control group (N=99)		Mean difference in change between groups, mixed models	
Change from Baseline	N	Mean Change (95% CI)	N	Mean Change (95% CI)	Adjusted* (95% CI)	p-value
Change in Constipation Score						
Baseline to Week 6	57	-1.2 (-2.11, -0.33)	82	-0.3 (-1.05, 0.48)	-0.89 (-2.03, 0.26)	0.1273
Baseline to Week 24	56	-1.1 (-2.15, -0.1)	81	-0.3 (-1.08, 0.45)	-0.88 (-2.03, 0.27)	0.1308

*Adjusted for Baseline value, Centre, Mobility (Walking unaided, Aided walking, wheelchair bound) and Sex. Centre was used as a random factor

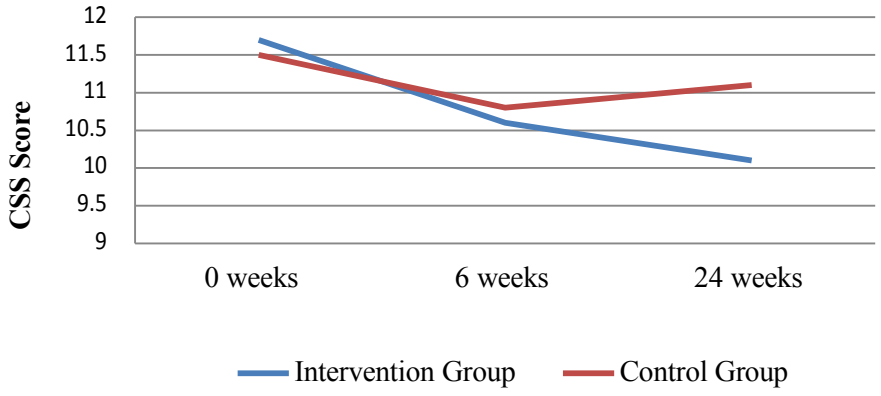

Figure 6. Change in Total Score of the CSS over time

Qualiveen Bladder Questionnaire

At baseline both groups demonstrated moderate effects of bladder dysfunction on their overall quality of life with a total Qualiveen Total score in the Intervention Group of 1.8 (SD 1.10) and the Control Group of 2.0 (SD1.20). The results in all four domains of the Qualiveen i.e. Bother with Limitations, Frequency of Limitations, Fears and Feelings related to urinary problems, were also similar in both groups There were no significant differences between groups in the change from Baseline to Week 6 or 24 in the Qualiveen Bladder Questionnaire score (Table 7).

Table 7. Analysis of change from baseline in Qualiveen Bladder Questionnaire score

	Intervention group (N=90)		Control group **(N =99)**		Mean difference in change between groups, mixed models	
Change from Baseline	N	Mean Change (95% CI)	N	Mean Change (95% CI)	Adjusted* (95% CI)	p-value
Qualiveen Total bladder score						
Baseline to Week 6	61	0.8 (-0.74-2.38)	85	1.4 (0.26-2.48)	-1.09 (-2.89-0.70)	0.2306
Baseline to Week 24	57	0.6 (-1.2-2.43)	81	0.5 (-0.89-1.96)	-0.58 (-2.74-1.58)	0.5968

*Adjusted for Baseline value, Centre, Mobility (Walking unaided, Aided walking, wheelchair bound) and Sex. Centre was used as a random factor

EQ-5D-5L – Quality of Life Outcomes

Chapter 4 the Health Economics Section summarises all the results of the EQ-5D-5L.

NBD PROM Questionnaire

There were no significant changes in any of the outcomes from the NBDS PROM. All results are summarised in Table 8.

Table 8. Summary of NBD patient reported Outcome Measure Questionnaire data

	Intervention Group (N=90)		Control Group **(N =99)**		Mean difference in change between groups, mixed models	
Change from Baseline	N	Mean Change (95% CI)	N	Mean Change (95% CI)	Adjusted* (95% CI)	p-value
Neurogenic Bowel Dysfunction Score PROM Total Score						
Week 6	53	0.3 (-1.34, 1.9)	82	1.0 (-0.8, 2.01)	-1.04 (-2.72, 0.64)	0.2216
Week 24	53	-0.8 (-2.62, 1.04)	77	0.3 (-0.85, 1.47)	-1.46 (-3.43, 0.52)	0.1468
Neurogenic Bowel Dysfunction Score PROM Quality of Life Score						
Week 6	54	0.6 (-0.21, 1.47)	83	0.4 (-0.22, 1.01)	0.04 (-0.93, 1.01)	0.9387
Week 24	56	-0.2 (-1.17, 0.81)	80	0.3 (-0.45, 0.97)	-0.70 (-1.82, 0.43)	0.2239
Neurogenic Bowel Dysfunction Score PROM Faecal Incontinence Score						
Week 6	61	0.0 (-0.51, 0.48)	87	0.3 (-0.03, 0.68)	-0.49 (-1.03, 0.05)	0.0768
Week 24	57	-0.1 (-0.69, 0.52)	82	0.4 (-0.05, 0.78)	-0.39 (-1.01, 0.23)	0.2117
Neurogenic Bowel Dysfunction Score PROM Symptom Score						
Week 6	59	-0.2 (-0.89, 0.45)	84	0.2 (-0.2, 0.68)	-0.42 (-1.12, 0.29)	0.2469
Week 24	56	-0.4 (-1.04, 0.22)	80	-0.2 (-0.66, 0.31)	-0.26 (-0.97, 0.46)	0.4779

*Adjusted for Baseline value, Centre, Mobility (Walking unaided, Aided walking, wheelchair bound) and Sex. Centre was used as a random factor

Bowel Diary Data

Within the SAP we identified the most important data to be analysed in the Bowel Diary data were the Number of days passing stool, Time spent on toilet and Percentage of normal stools.

Each participant was required to complete 8 weeks of bowel diaries (Baseline, Weeks 1-6 and Week 24). Overall these were well completed and compliance was high. For example, frequency of passing of stool was completed by 88/90 (97.7%) and 98/99 (98.9%) pre-intervention; 68/90 (75.5%) and 89/99 (89.8%) at 6 weeks, and by 57/90 (63%) and 81/99 (81%) at Week 24 for the Intervention and Control Groups respectively.

Stools passed per week

The mean frequency of stools passed per week at baseline was 3.9 (SD 1.68) and 4.0 (SD 1.74) in the Intervention and Control Groups respectively. At Week 6 this was increased to 4.3 (SD 1.87) in the Intervention Group and was reduced to 3.9 (SD 1.81) in the Control Group; at Week 24 to there was no change in either group 4.3 (SD 1.88) and 3.9 (SD 1.89) respectively. Figure 7 is a line graph visually showing the change over time within the two groups.

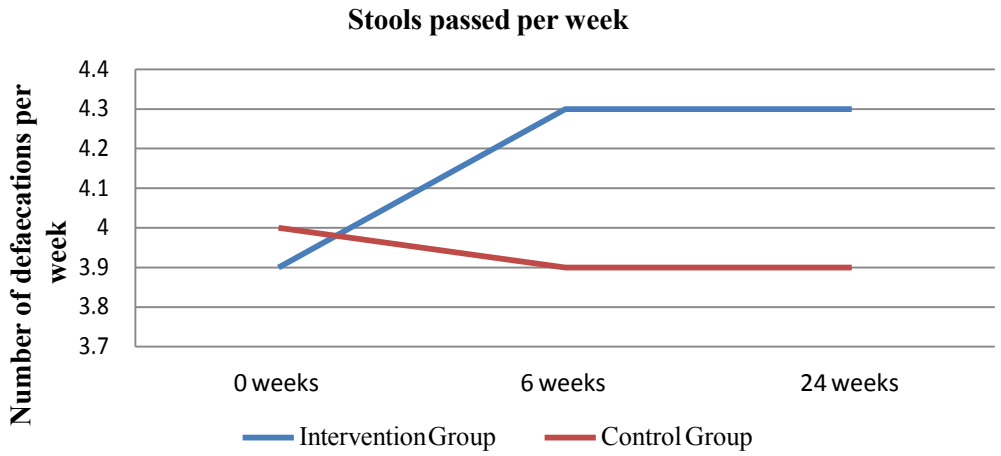

Figure 7. Change in the mean number of stools passed per week

There was a statistically significant difference between groups in the change in number of stools passed from baseline to Week 24 (Table 90). The difference between the groups was 0.62 (95% CI 0.03 to 1.21, p=0.039). As there was some inconsistency in completion of the diaries the analysis of change values were derived from a combination of two questions how often did you pass stool and type of stool to give one answer on frequency i.e. if one or other completed then this was taken as having passed stool, if neither then no stool was passed. Figure 8 highlights very little change in the first 5 weeks.

Table 9 Analysis of change from baseline in the number of stools passed per week

	Intervention group (N=90)		**Control group (N =99)**		Mean difference in change between groups, mixed models	
Change from Baseline	N	Mean Change (95% CI)	N	Mean Change (95% CI)	Adjusted* (95% CI)	p-value
Stools passed (/week) (Adjusted to combine number and type of stool if data inconsistent)						
Baseline to 6 weeks	67	0.4 (0.07, 0.68)	88	0.0 (-0.34, 0.39)	0.38 (-0.08, 0.85)	0.1036
Baseline to 24 weeks	56	0.1 (-0.34, 0.51)	80	-0.5 (-0.88, 0.02)	0.62 (0.03, 1.21)	0.039

*Adjusted for Baseline value, Centre, Mobility (Walking unaided, Aided walking, wheelchair bound) and Sex. Centre was used as a random factor.

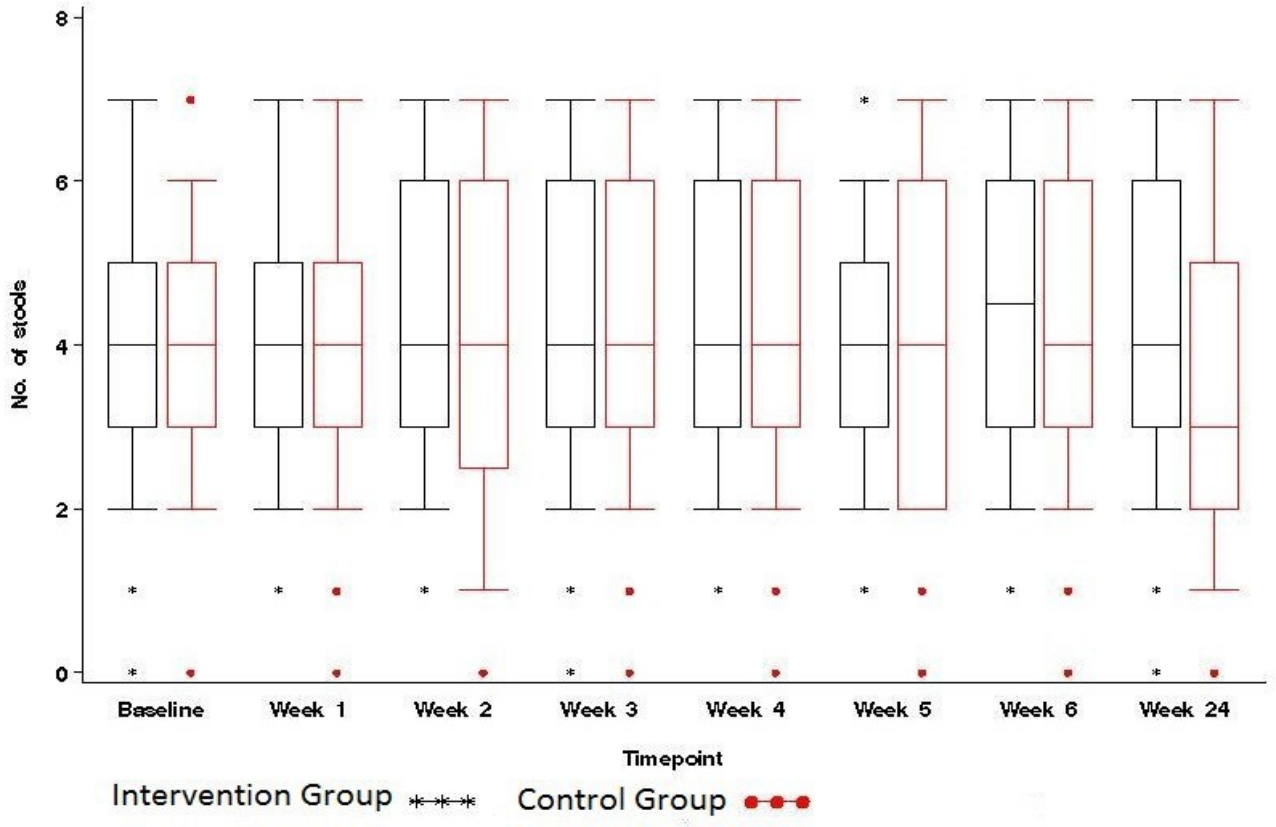

Figure 8. Box and whisker plot of number of stools passed

Time spent on the toilet

At baseline those in the Intervention Group spent a mean of 75.6 (SD 69.60) minutes and the Control Group 75.8 (SD 74.36) minutes per week on the toilet; at Week 6, 77.9 (SD 73.26) and 85.0 (SD 88.52) minutes per week respectively; and at Week 24 78.2 (SD 92.43) and 77.0 (SD 68.51) minutes per week respectively. There was no statistically significant difference between groups in the mean change in time spent going to the toilet between baseline and either time-point (Table 101)

Table10 Analysis of change from baseline in time spent on the toilet.

	Intervention group (N=90)		Control group (N =99)		Mean difference in change between groups, mixed models	
Change from Baseline	N	Mean Change (95% CI)	N	Mean Change (95% CI)	Adjusted* (95% CI)	p-value
Time spent on the toilet (min/ week)						
Baseline to 6 weeks	60	-0.7 (-15.7, 14.39)	80	9.8 (-5.28, 24.95)	-7.92 (-29.0, 13.17)	0.4588
Baseline to 24 weeks	50	-6.5 (-21.86, 8.78)	71	(-19.71, 12.17)	-3.35 (-23.1, 16.4)	0.7377

*Adjusted for Baseline value, Centre, Mobility (Walking unaided, Aided walking, wheelchair bound) and Sex. Centre was used as a random factor

Type of Stool

For each stool passed participants were asked the type as per the Bristol Stool Chart (Chapter 2, Figure 2). Using Type 3 and 4 as normal, and Type 1 & 2 and no stool per week as constipated, there was a reduction in the percentage who were constipated in the Intervention Group from 61.6% at Baseline to 55.4% at Week 24 and from 59.0% to 58.9% in the Control Group. The percentage passing normal stool types 3 or 4 was 20.2% in the Intervention Group and 17.5% in the Control Group at Baseline and at Week 24 this was 23.9% and 22.8% respectively (Appendix 6).

Medications used in AMBER for Bowel Management (information from medication form)

At baseline 67 (74%) participants in the Intervention Group and 80 (80%) participants in the Control Group were on at least one medication with numbers of medications ranging from 1 to 35. The number of these participants on medication for management of their bowel symptoms were 44 (i.e. 44/67:66%) in the Intervention Group and 54 (i.e. 54/80:68%) in the Control Group. Laxido, Movicol and Docusate appeared to be the most popular medications used in both groups with suppositories only being used by approximately 9% of participants in each group.

Forty-Four participants were on zero medications (24 in intervention and 20 in the control groups) at the start of the trial.

During the course of the study, 32 participants started new medications in the Intervention Group versus 44 participants in the Control Group with nearly twice as many new medication entries recorded in the Control Group compared to the intervention group (69 versus 135). Thirteen participants in the Intervention group had taken at least one additional medication for bowel management with 19 different entries recorded in total (e.g. one patient had 5 entries for 4 different laxatives). In the Control Group 12 participants started new medications for their bowels with 33 different entries (several reported 3-4 additional bowel medications, one had 12 entries, 8 different bowel medications and 4 for glycerine suppositories).

At the end of the study, 15 participants in the Intervention Group had stopped taking some of their bowel management medications (18 entries in total) and 13 participants had stopped in the Control Group (35 entries). There were still 38 participants who were not on any form of medication (20 in intervention and 18 in the control groups) at the study end.

Ano-rectal physiology and transit test results

University College London (UCL) was the only site in the AMBER study to recruit to a pilot sub-study to determine if any information about the mechanism of action of abdominal massage could be determined through anorectal physiology and colonic transit tests which are routinely undertaken at this site. Participants had a test at Baseline and a repeat test at Week 24. All participants from UCL took part in the sub-study.

A total of 26 participants were randomised at UCL, however two post-randomisation exclusions occurred. Twenty-four participants completed all baseline outcomes for the main study. Of these, 23 participants, 2 male (8.7%) and 21 female (91.3%), mean age 53.5 (SD 12.59) years, 11 in the Intervention Group and 12 in the Control Group, underwent baseline transit tests. There was no baseline transit test data for one of the 24 participants. Three participants withdrew from the study during the 6 weeks of intervention and a further one participant was lost to follow up (could not be contacted for the Week 24 follow-up and did not return any patient reported outcomes). A further 8 participants withdrew from having the repeat tests at Week 24, leaving 12 participants with Week 24 transit and physiology results. One of these participants had no baseline transit data, thus 11 sets of baseline and Week 24 transit test data were available for analysis.

There was no difference between the groups with respect to changes in the duration of bowel symptoms, faecal incontinence, infrequent emptying, pain or bloating (See Supplementary data for more information). The base-line data indicated that 65.2% (n=15/23) of the participants who underwent the transit test had slow transit, 6 (54.5%) Intervention and 9 (75%) in Control.

Table 11 shows there was no significant difference in respect of the Total Markers mean difference in change between the Groups although there was a possibility that Groups were not well matched at Baseline with a Median of 17 (Range 0-54) in the Intervention Group and in the Control Group the Median was 47 (Range 0.60). The small number of participants mean the confidence interval is wide. The markers in the rectosigmoid were relatively well matched at Baseline; Median 10 (range 0-46) in the Intervention group and a Median 12.5 (range 0-35) in the Control Group.

Table 11. Radio Transit Total Markers data summary

	Intervention Group		Control Group		Mean difference in change between groups, mixed models	
Change from Baseline	N	Mean Change in number of markers (95% CI)	N	Mean Change in number of markers (95% CI)	Adjusted* (95% CI)	p-value
24 weeks	5	13.2 (-20.04, 46.44)	6	-7.8 (-20.29, 4.63)	15.7 (-37.69, 69.01)	0.4846

*Adjusted for Baseline value, Centre, Mobility (Walking unaided, Aided walking, wheelchair bound) and Sex. Centre was used as a random factor

Notwithstanding the substantial numbers who failed to complete the post test at Week 24; (n=5 in the Intervention Group and n=6 in the Intervention Group) the pre-treatment versus Week 24 change was 16 (range –6 to 32) and –5.0 (Range –13 to 17) respectively which may be explained that in the Intervention Group the massage was moving content to the distal colon if not necessarily triggering evacuation.

The difference at baseline for the Total Markers and markers in the left and right colon i.e. groups not matched at base-line for these outcomes, as well as the numbers not completing the test at Week 24 make it impossible to differentiate between changes due to regression to the mean or actual change.

Anorectal Pressure tests and Anal and rectal sensation and capacity

The small numbers who completed the tests at Week 24 mean that the sample size is too small to draw conclusions.

Adverse Events

A total of 84 Adverse Events (AEs) were noted in the trial, 28 in the Intervention group and 56 in the control group. Table 12 summarises this information along with the numbers of participants affected in each group.

Table 12. Adverse Events reported

	Intervention Group	Control Group	Total
All participants	91	100	191
Participants with adverse events	19	30	49
Number of adverse events	28	56	84
Of which, serious adverse events	3	6	9

Appendix 7 is a summary of all the adverse events. Five AE's were reported as *"possibly"* related to the intervention however two were reported in the control group (UTI and diarrhoea) and as they had no intervention, the fact there are 2 AEs were classed as *"possibly"* related to the intervention is deemed as an error in the site reporting of these. For the three possibly related adverse events reported in the intervention group, 2 were for one patient who had two UTIs both of which resolved within a week, and one participant had reflux and went to A&E but was not admitted. Both these participants were still continuing with the massage at 24 weeks despite these reported adverse events.

Additional AE information on all AEs (reported by primary System Organ Class (SOC) and Preferred Term (PT) can be found in the supplementary data provided with this report.

Summary of Serious Adverse Events

From the 84 reported AEs, nine were classified as a Serious Adverse Event (SAE). A summary of the SAEs are reported inAppendix 7. Two of these events were a hospitalisation due to an MS relapse (one in each study group) and one was a fall but considering the study cohort these are not surprising events. None were related to the trial and all were resolved.

Secondary Analysis

In a secondary analysis, using multiple imputation for the missing data, of the primary outcome, baseline variables age, gender, BMI, type of MS, site disease duration (years since diagnosis), cognitive symptoms of MS and minimisation variable level of mobility (walking unaided, aided or wheelchair bound) were included in the model. Table 15 shows the results adjusted for all variables and this indicated a similar result as found in the primary analysis with no significant difference between intervention and controls. For site with Edinburgh taken as the reference site there was no statistical significant difference between the sites (p=0.8326) although Sheffield, Salford, Lincoln, Leeds and John Radcliffe reporting slightly better results when compared to Edinburgh. Regression analysis also indicates that there is more likely to be a benefit in the Intervention Group for those walking unaided or aided responding better than wheelchair bound, while those of greater age and higher Body Mass Index (BMI) also did slightly better. Duration of MS did not seem to be important but those with relapsing remitting MS responded more positively than those with primary progressive MS. Cognition severity indicated that those with mild or no impairment did better than those with severe. Consistent with other findings males do significantly better (Mean difference - 2.789, 9% CI -5.179 to -0.399; p=0.0226).

Table 13. Secondary analysis: Primary outcome NBD score adjusted for all baseline variables

Variable	Estimate	Confidence interval lower	Confidence interval upper	p-value
Intervention vs Control	-1.060	-2.976	0.855	0.2751
Centre vs. Edinburgh				0.8326
Southern General Hospital, Glasgow	0.135	-4.334	4.604	
Royal Victoria Hospital, Newcastle upon Tyne	2.411	-2.397	7.218	
University College Hospital, London	0.997	-3.614	5.608	
Royal Preston Hospital, Preston	1.868	-2.996	6.732	
The Walton Centre, Liverpool	1.411	-3.704	6.526	
John Radcliffe Hospital, Oxford	-0.257	-4.901	4.387	
Leeds Community Healthcare NHS Trust	-0.326	-5.321	4.668	
United Lincolnshire Hospitals NHS Trust	-0.034	-4.845	4.778	
Salford Royal Hospital NHS trust	-0.687	-5.481	4.107	
Sheffield Teaching Hospitals NHS Trust	-1.594	-6.223	3.034	
Northampton General Hospital	1.893	-3.560	7.347	
Baseline NBD Score (+1 unit)	0.327	0.137	0.516	0.0009
Minimisation variable Mobility vs Wheelchair bound				0.9560
Walking unaided	-0.218	-3.476	3.040	
Aided walking	-0.425	-3.525	2.674	
Age [+1 year]	-0.097	-0.211	0.018	0.0972
BMI (+1 kg/m^2)	-0.042	-0.207	0.124	0.6171
Male vs Female	-2.789	-5.179	-0.399	0.0226
Variable	**Estimate**	**Confidence interval lower**	**Confidence interval upper**	**p-value**
Duration of MS [+1 years since diagnosis]	0.046	-0.069	0.160	0.4309
Cognitive Status vs Severe				0.7719
None	-0.754	-6.832	5.323	
Mild	-1.720	-7.722	4.282	
Moderate	-0.709	-6.833	5.415	
Type of MS vs Primary Progressive				0.5537
Type of MS: Benign	-1.515	-10.071	7.041	
Type of MS: Relapsing Remitting	-2.525	-6.031	0.980	
Type of MS: Secondary Progressive	-1.749	-5.325	1.826	

Sensitivity analysis

Sensitivity analysis was carried out with multiple imputation of the Primary Outcome NBD and a similar result to the primary analysis was found (Difference in change Intervention vs Controls -1.266 95% CI -2.936, 0.403; p = 0.1371) (see Table 16). Males however again demonstrated a greater beneficial effect (Males vs Females -2.280, 95% CI -4.478 to -0.083; p=0.0419)

Table 14. Sensitivity analysis of the primary analysis with multiple imputation of Primary Outcome NBD

			Confidence Interval		
Parameter	**Estimate**	**Std Error**	**lower**	**upper**	**p-value**
Intervention Group vs. Control Group	-1.266	0.852	-2.936	0.403	0.1371
Centre: John Radcliffe Hospital, Oxford	-0.084	2.289	-4.570	4.402	0.9708
Centre: Leeds Community Healthcare	-0.012	2.434	-4.784	4.759	0.9959
Centre: Northampton General Hospital	0.847	2.368	-3.794	5.488	0.7206
Centre: Royal Preston Hospital, Preston	1.062	2.233	-3.315	5.438	0.6345
Centre: Royal Victoria Hospital, Newcastle	1.225	2.290	-3.263	5.712	0.5927
Centre: Salford Royal Hospital NHS trust	0.090	2.254	-4.328	4.508	0.9682
Centre: Sheffield Teaching Hospital	-1.622	2.247	-6.026	2.783	0.4706
Centre: Southern General Hospital, Glasgow	-0.083	2.159	-4.313	4.148	0.9694
Centre: The Walton Centre, Liverpool	1.039	2.487	-3.835	5.914	0.6760
Centre: United Lincolnshire Hospitals	-0.468	2.304	-4.984	4.048	0.8391
Centre: University College Hospital, London	0.168	2.148	-4.042	4.378	0.9377
NDB Total score at baseline	0.356	0.090	0.181	0.532	<.0001
Minimisation variable Mobility: Aided walking	-0.192	1.420	-2.975	2.591	0.8924
Minimisation variable Mobility: Walking unaided	0.320	1.449	-2.521	3.161	0.8251
Male vs. Female	-2.280	1.121	-4.478	-0.083	0.0419

The repeated measures analysis (Table 15) was not significant for the primary outcome and all other outcomes except for the increased number of times participants felt their bowel to be emptied and the number of stools passed per week which were in favour of the Intervention. At 6 weeks (Mean Difference Intervention vs Controls was 0.98, 95% CI 0.36 to 1.61; p=0.03902) and (0.56 95% CI 0.03 to 1.10; p=0.039) respectively. This effect was decreased for both outcomes at 24 Weeks but was still statistically significant over all time periods.

Table 15. Summary of repeated measures analysis of primary and secondary outcomes

	6 weeks		24 weeks		Overall
	Intervention - Controls		Intervention – Controls		
Outcome	**LS Mean (95% CI)***	**p-value***	**LS Mean (95% CI)***	**p-value***	**p-value***
NBD Score	-1.16 (-2.84, 0.53)	0.179	-0.54 (-2.26, 1.17)	0.535	0.254
Constipation score	-0.88 (-1.99, 0.23)	0.121	-0.53 (-1.64, 0.58)	0.349	0.157
Time spent on toilet	-0.42 (-21.5, 20.6)	0.969	-9.70 (-29.3, 9.9)	0.331	0.545
No attempts per week	1.31 (-0.66, 3.29)	0.192	1.01 (-0.83, 2.86)	0.281	0.138
No Times emptied bowels	0.98 (0.36, 1.61)	0.002	0.48 (-0.11, 1.07)	0.108	0.007
No Stools / week	0.56 (0.03, 1.10)	0.039	0.32 (-0.18, 0.82)	0.215	0.026
Qualiveen Bladder Score	-0.24 (-2.17, 1.69)	0.809	-0.87 (-2.76, 1.01)	0.363	0.498
EQ 5D 5L Visual Analogue Score	4.30 (-2.05, 10.65)	0.184	0.67 (-5.59, 6.92)	0.834	0.374
EQ 5D 5L UK Health Index Score	0.003 (-0.05,0.065)	0.916	0.004 (-0.056, 0.065)	0.885	0.888
NBD PROM Faecal score	-0.37 (-0.95, 0.20)	0.203	-0.43 (-0.99, 0.13)	0.136	0.107
NBD PROM QOL	-0.67 (-1.68, 0.34)	0.192	-0.06 (-1.07, 0.95)	0.907	0.403
NBD PROM Symptom Score	-0.29 (-0.99, 0.41)	0.415	-0.43 (-1.12, 0.25)	0.214	0.226
NDB PROM Total score	-1.40 (-3.15, 0.35)	0.117	-1.05 (-2.79, 0.68)	0.234	0.106

*Mixed model repeated measures least squares estimates

Change in Laxative Use (OR – Odds Ratio)

Outcome for the regular use of laxatives or drops at Week 6 vs not the OR = 2.37 (95% CI 0.87, 6.46), p = 0.092 using ordinal regression adjusted for all baseline variables (Baseline use, Centre, Age, Gender, Mobility, BMI, duration of MS, type of MS, and cognitive status). Outcome for the regular use of laxatives or drops vs not at Week 24 the OR = 1.62 (95% CI 0.74, 3.55), p = 0.229 using ordinal regression adjusted for all baseline variables (Baseline use, Centre, Age, Gender, Mobility, BMI, duration of MS, type of MS, and cognitive status). Although the Odds ratios were not significant there is some evidence that the Intervention group is twice as likely to achieve a lower level of laxative use than the standard group (see Table 16).

Table 16. Secondary Analysis of Regular use of laxative drops or tablets at all time points NBD Score

	Intervention Group		Control group		Total	
Variable	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Regular use of laxative drops or tablets						
Pre-intervention						
Missing	0	(0.0%)	0	(0.0%)	0	(0.0%)
No regular use	41	(45.6%)	48	(48.5%)	89	(47.1%)
Regular use of laxative drops or tablets	43	(47.8%)	47	(47.5%)	90	(47.6%)
Regular use of both laxative drops and tablets	6	(6.7%)	4	(4.0%)	10	(5.3%)
Total	90	(100.0%)	99	(100.0%)	189	(100.0%)
Week 6						
Missing	0	(0.0%)	1	(1.1%)	1	(0.6%)
No regular use	34	(53.1%)	48	(53.3%)	82	(53.2%)
Regular use of laxative drops or tablets	27	(42.2%)	37	(41.1%)	64	(41.6%)
Regular use of both laxative drops and tablets	3	(4.7%)	4	(4.4%)	7	(4.5%)
Total	64	(100.0%)	90	(100.0%)	154	(100.0%)
Week 24						
Missing	0	(0.0%)	0	(0.0%)	0	(0.0%)
No regular use	43	(59.7%)	51	(56.7%)	94	(58.0%)
Regular use of laxative drops or tablets	26	(36.1%)	35	(38.9%)	61	(37.7%)
Regular use of both laxative drops and tablets	3	(4.2%)	4	(4.4%)	7	(4.3%)
Total	72	(100.0%)	90	(100.0%)	162	(100.0%)

Post-HocAnalysis

The following descriptive analysis (and where indicated further statistical analysis) focuses on questions within questionnaires and on further bowel diary data on symptoms that were identified as being important to participants and/or were identified in other analyses as significantly changed between Groups

Neurogenic Bowel Dysfunction Score – those with constipation at baseline i.e. ≥11

As the overall level of constipation at baseline was rated as mild in both groups according to the NBS score (Baseline the Total score for the Intervention arm was Mean 7.6 (SD 5.31) Median 6.0 (Range 0-21) and in the Control Group 8.6(SD 5.08) Median 9.0 (Range 0-22) we repeated our analysis with only those with NBD score at baseline of 11 or more (results in Table 17).

Table 17. Neurogenic Bowel Dysfunction Score for patients with an NBD score at baseline>=11

	Intervention Group							Control Group						
Time Point	**N**	**Mean SD**	**1st Quartile**	**Median**	**3rd Quartile**	**CL**	**upper CL**	**N**	**Mean SD**	**1st Quartile**	**Median**	**3rd Quartile**	**lower CL**	**upper CL**
Intervention at 6 weeks	20	12.3 6.4	7.0	13.0	18.5	9.3	15.2	28	10.7 4.7	7.5	10.5	13.5	8.9	12.5
Intervention at 24 weeks	22	9.0 6.3	4.0	9.5	12.0	6.2	11.8	28	9.9 5.4	6.0	9.5	13.0	7.8	12.

The Univariate analysis and Linear Regression analysis can be reviewed in the supplementary data. The numbers in both groups was reduced and the only evidence of any effect was for those who had MS longer at Week 6 (F 4.30, p=0.043, estimate 0.153, T-Value 2.07, p=0.0437. lower CI 0.004, Upper CI 0.302).

Frequency of defaecation as per Question 1 in NBD score

There was an increase in the number of participants passing stool daily from Baseline to Week 24 in the Intervention Group (12.2% to 23.6%), with a smaller increase in the Control Group (16.2% to 20.0%). The Intervention Group had a small decrease in the percentage passing stool less than once per week (6.7% to 5.6%), compared to an increase in the control group (7.1% to 12.2%).

Frequency of defaecation as per the question in the Constipation Score Questionnaire

The percentage of participants in the Intervention Group who were passing stool 2 or more times per week was 92.1% and in the Control Group it was 88.6%; passing stool less than once a week was 6.6% in the Intervention Group and 10.1% in the Control Group. At Week 24 the numbers passing more than 2 times a week was increased to 94.9% in the Intervention Group and had decreased in the Control Group to 80.7%; 3.4% of the Intervention Group were now passing less than once a week and in the Control group this had increased to 16.8%.

Feeling of incomplete evacuation as per the question in the Constipation Score Questionnaire

The percentage of participants in the Intervention Group who *'felt incomplete evacuation'* "never" was 6.7% at baseline and in the Control Group it was 9.1%; at Week 24 this increased to 15.5% in the Intervention Group and decreased from to 8.4% in the Control Group. At Baseline 21.3% in the Intervention Group and 20.3% in the Control Group '*always felt incomplete evacuation*'; at Week 24 this decreased to 3.4% in the Intervention Group and to 10.8% in the Control Group.

Bowel Diary Data

Attempts to Pass Stool

At Baseline the Intervention Group had 10.4 (SD 6.73) and the Control Group had 8.6 (SD 5.22) attempts to pass stool, at Week 6 this was 11.3 (SD 7.31) and 8.9 (SD 6.00) attempts respectively and at Week 24 the number of attempts to pass stool was 10.7 (SD 7.16) and 8.3 (SD 5.09) respectively.

As can be seen in Table 18 and Figure 9 the mean changes between baseline and Weeks 6 and 24 for attempts to empty the bowel were not statistically significant between groups.

Table 18. Attempts to pass stool per week

	Intervention Group (N=90)		Control Group (N=99)		Mean difference in change between groups, mixed models	
Change from Baseline	N	Mean Change (95% CI)	N	Mean Change (95% CI)	Adjusted* (95% CI)	p-value
Attempts to empty the bowels (/ week)						
6 weeks	62	0.2 (-1.49, 1.84)	84	0.4 (-0.83, 1.66)	1.08 (-0.81, 2.96)	0.2608
24 weeks	52	-0.9 (-2.82, 1.02)	75	-0.5 (-1.96, 1.0)	1.14 (-0.92, 3.19)	0.2770

*Adjusted for Baseline value, Centre, Mobility (Walking unaided, Aided walking, wheelchair bound) and Sex. Centre was used as a random factor

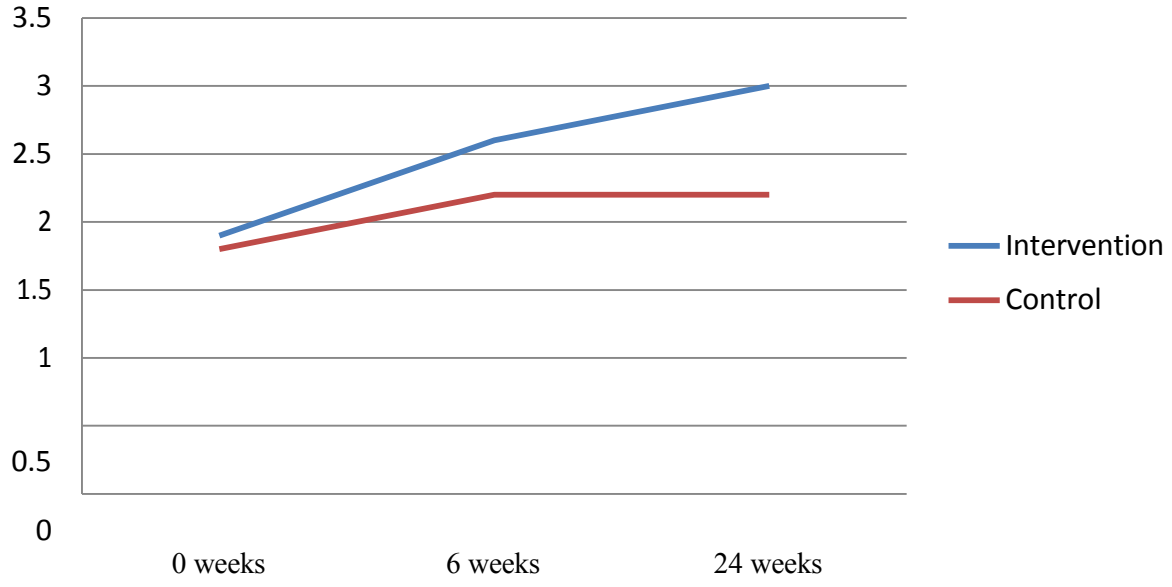

Figure 9. Frequency of Feeling of successful evacuation

The number of times per week the participants felt that they had a complete evacuation at baseline was 1.9 (SD 2.2) and 1.8 (SD 1.73) for the Intervention and Control groups respectively. At 6 weeks this was 2.6 (SD2.2) and 2.2 (SD 2.0), and at Week 24 was 3.0 (SD and 2.2 (SD 2.14) Intervention Group/Control Group respectively.

There was a statistically significant difference between groups in the change in number of complete evacuations per week from baseline to Week 24 (p=0.002). The intervention group

had on average increased the number of complete evacuations per week by 1.08 more than the control group. This, though this was a post-hoc analysis.

Table 19. Number of times complete evacuation per week reported

	Intervention Group (N=90)		Control Group (N =99)		Mean difference in change between groups, mixed models	
Change from Baseline	N	Mean Change (95% CI)	N	Mean Change (95% CI)	Adjusted* (95% CI)	p-value
Number of times had feeling of complete evacuation per week						
6 weeks	62	0.8(0.4, 1.2)	84	0.2 (-0.2, 0.6)	0.48 (-0.10, 1.06)	0.104
24 weeks	52	1.2(0.6,1.8)	75	0.3 (-0.1, 0.7)	1.08 (0.41, 1.76)	0.002

*Adjusted for Baseline value, Centre, Mobility (Walking unaided, Aided walking, wheelchair bound) and Sex. Centre was used as a random factor

Other Diary Data

Analysis of other data provided by the self-completed bowel diary was not statistically tested as per SAP (e.g. frequency of faecal incontinence, use of digital stimulation; type of stool) and no change was identified between groups to warrant post hoc analysis.The Bowel diary question on laxative use asked if laxative use was the same, less or more. This was difficult to analyse as it was not being compared to baseline but to the week before.

Adherence to the Intervention (Massage diary and nurse weekly telephone calls)

All participants received weekly telephone calls from the research nurse during the 6 weeks of intervention and again at Week 24. The aim of the calls was to support fidelity to the trial protocol. There was good response to the follow-up telephone calls made by research staff at sites; 81% of participants in the Intervention Group and 86% in the Control Group were

reached at Week 24 and data collected during the telephone calls.

According to information collected during the follow-up calls, 72.6% to 83.3% of participants in the Intervention Group administered the massage themselves throughout the 6 weeks of intervention; 10.3% to 14.1% a carer undertook the massage. Some data was missing or massage was not undertaken in 2.6% of cases.

According to the Bowel Diary records which also recorded when the massage was undertaken in the Intervention Group the mean number of days on which massage was performed per week was 5.2 (SD 1.88). This varied little over the 6 weeks of intervention (Week 6 mean 5.4, SD 1.75). At Week 24 those still doing the massage (n = 57, 82%) were undertaking it on average 3.2 times a week (SD 2.83). Mean time spent on the massage during Weeks 1-6 was 72.5 (SD 4.0) and at Week 24 it was 55.8 minutes SD (40.0).
Participants were shown how to perform the massage lying down, semi-lying down or sitting up. Information on the choice of position utilised, in addition to the time of day the massage was performed, was collected during the 6 weeks of the intervention. During weeks 1-6, 58-64% of participants performed the massage lying down, 16-24 % semi-lying down and 1-4% sitting up.

Morning massage administration seemed to be the preferred time (46-56% of all participants), then evening (26-31%), with afternoon administration being least common (4-6%).

Information from Nurse weekly telephone calls

Reasons for discontinuing the intervention, as reported in the final Week 24 telephone call with the Research nurse (n=77 interviews; 20 discontinued) included no benefit 8(10%), burden on carer 1(1.3%) and too difficult 5 (6.5%) and the rest gave no reason or were missing

Adherence to lifestyle – 20% of the Intervention Group and 30% of the Control Group stated they made at least one change to their lifestyle as part of the optimised bowel care information. Compared to the Intervention Group more in the Control Group changed their diet during weeks 1 to 4 but did not seem to continue with this, but continued to alter their fluid intake and took more exercise. The numbers who changed their position for defaecation was similar in both groups.

Approximately 50% of participants in the intervention arm reported a change in their bowel habits compared to 38% in the control group at Week 1 and this difference was mirrored at Week 24 with approximately 43% in the intervention versus 31% in the control reporting a change in bowel habits. Changes reported more frequently in the Intervention Group were more frequent bowel movements, less time spent on the toilet and had softer stools compared to the control group at Week 1 and Week 24.

NOTE: The AMBER study full set of descriptive statistics is provided with this report as supplementary material.

NBD PROM (NBIS)

Analysis of the new neurogenic bowel symptom score was undertaken for further validation and the analysis carried out is contained within the supplementary date supplied with this report.

The new neurogenic bowel PROM (NBIS) showed only moderate repeatability in the control group for the Amber Study. However, this was over a longer time period than usually used for test-retest stability, and it is possible that the MS bowel symptoms had genuinely changed in the control group. It is known that MS bowel symptoms are variable over time. Repeat of this test-retest with a shorter time between the completions and possibly asking participants if they perceive that their symptoms changed or not is recommended.

When compared against other bowel symptom scores such as the NBDS and the Wexner score, a high correlation was found for most items, suggesting good criterion validity for the new questionnaire. It was also highly correlated with the EQ-5D quality of life score, but not the EQ-5D VAS. NBIS was strongly correlated with the primary outcome measure NBDS. As the new questionnaire was developed after extensive qualitative work with people with neurogenic bowel dysfunction, including MS, this lends credibility to both scores. However, neither score showed a significant difference between our intervention and control groups, so there is no evidence that one is more responsive to change that the other. Further work is needed to determine which score patients find better reflects what is important to them. As our trial found no significant difference between groups, we are not able to recommend either score as being more or less sensitive to change. We did not find anything to suggest an advantage to either questionnaire and both had similar completion rates.

However as discussed some questions within the NBD (primary outcome) were difficult for some patients to fully understand e.g. digital stimulation, use of drops whilst in the new questionnaire the language was better but the whole questionnaire was felt to be too long.

CHAPTER 4 Health Economic Evaluation

Economic evaluation

The aim of the AMBER trial was to determine the effectiveness and cost effectiveness of abdominal massage (intervention) as part of an adjunct to the control of optimised bowel care in people with Multiple Sclerosis who have NBD. This chapter gives the results of a formal economic evaluation of the AMBER intervention compared to control from an NHS and patient cost perspective. Health related quality of life (HR-QoL) data and health care resource use data was used to examine the following:

1. The cost of delivery for the patient groups.
2. The health care costs for participants in both trial groups.
3. HR-QoL through calculation of Utility values using the EQ-5D-5L.

Using the above information we calculated an incremental cost-effectiveness ratio and the probability of the intervention being cost-effective at different thresholds of willingness to pay per Quality Adjusted Life Year (QALY) gained.

Data related to the economic analysis

Abdominal massage costs

The intervention is described in Chapter 2. In this chapter, only costs that would be observed if the intervention was delivered in practice will be considered and trial related costs are not part of the analysis. In terms of the materials used for the training of the patients, it was estimated that the DVD production and the training materials provided would cost approximately £1 per participant. Research staff involved in AMBER confirmed that the training of participants would take approximately 30-45 minutes. If abdominal massage becomes an established intervention in the NHS, it is expected that NHS staff involved in training patients would usually be at an NHS pay grade 5, 6 or 7 (and could also be non-nursing staff).

For the purpose of this economic evaluation and based on the above information, an on-going cost of £90 per patient was calculated for the intervention and £0 costs were assumed for the controls. For the intervention this is calculated assuming a hospital based grade 6 nurse would provide this service for 50 minutes which comes at £89 cost per patient contact plus

patient since contact will typically take less than 50 minutes and this service can be provided by lower pay grade staff and non-nursing staff. Duration of contact was not recorded in the trial therefore we are unable to determine with certainty the exact length of these appointments and the highest possible length (50 minutes) was chosen for our baseline analysis. Furthermore, it was assumed that standard care involved no additional costs other than resource use therefore, zero was taken as the baseline cost for the control group even though in practice NBD sufferers would have access to services and that would involve some costs for the NHS. Moreover, in this trial the control group did get follow up calls and they were aware of the potential to be offered abdominal massage in the future. These were considered to be trial only costs and were not included in the cost-effectiveness analysis.

Health care resource use data

Resources used by the participants were recorded in the outcome questionnaires at Baseline, Week 6 and Week 24. Participants were asked to record use of NHS services and all contacts with health care professionals throughout the trial period and not just those they directly associated with bowel problems, these are presented in Appendix 11.

Health care costs

The information on resource use was combined with the unit cost of each resource to estimate the total cost of NHS resources used. Health service unit costs were valued using the most recent Department of Health resource cost data, at 2015-16 UK prices. The NHS resources that were included and their unit costs are shown in Appendix 10, along with the source of cost information. The cost of drugs consumed by participants only includes drugs prescribed by the participants' general practitioner (this is not shown in the table). The British National Formulary (BNF) edition 66 was consulted for the unit cost of individual drugs prescribed to participants.

NHS resource use costs were calculated using unit costs as sown in Appendix 10, hospitalisation refers to the cost of an average impatient stay in a hospital in England and Wales as estimated in the PSSRU. Patients did not report length of stay but only if they have been admitted to hospital. Therefore, we assume that on average patients stayed in hospital for the average duration of stay in England and Wales and we apply the cost of £1,609 to each reported case of hospitalisation. The total resource use related costs for the NHS in each trial group at each timepoint are also shown in Appendix 10.

NHS resource use and associated costs were not statistically different between the two groups. Reported resource use suggests that there was little difference between the groups in terms of NHS costs related to resource use. The impact of the costs at 6 weeks and 24 weeks is investigated further in the cost-effectiveness analysis. Costs at 6 weeks includes all recourse use from baseline up to the 6 week follow up point. Costs at 24 weeks includes all recourse use from the 6 week follow up point to the end of the trial at 24 weeks. Baseline costs are not included in the cost-effectiveness analysis since they take place before the trial started but are used to show there is no statistical difference between the two groups at baseline.

As standard practice and as part of the economic evaluation for this trial and we collected information on NHS resource use, prescribed medication and out of pocket costs. For reasons unknown to us completion of prescribed medications and out of pocket costs was poor resulting in many missing observations. Patients did have the option of reporting zero costs in these questions but the majority did not respond. Given the reported medication and out of pocket costs were very low, similar between the two groups and their poor quality we decided to only use intervention costs and NHS resource use costs in the economic evaluation that follows and excluded other costs. In general few patients reported drug related costs resulting in many missing observations Due to the low numbers that responded to these questions

we do not take into account these costs in the cost-effectiveness analysis that follows. Drug prescription costs in the intervention group were driven by a one participant who was prescribed very expensive medicinal cannabis based drugs. For example, if we remove this participant from the calculations below the mean £187.25 cost per patient decreases to £18 spending per patient. This patient reported a cost of £1,372 in the period between 6 and 24 weeks follow up vastly inflating the reported mean of £187.25 at week 24 in Table 20. Testing the equality of means at weeks 6 and 24 using t-tests (t=1.16 and t=0.79 respectively) suggest there is no significant difference between the patients who responded to these questions on drug related costs.

Table 20. Prescribed Medication by trial group per patient spending

	Intervention Group (£)		**Control Group (£)**	
	Total		**Total**	
Per patient Cost at Baseline	£3.20	SD: 0	£5.08	SD: 0.19
Per patient Cost at Week 6	£11.17	SD: 6.00	£22.83	SD: 21.59
Per patient Cost up to Week 24 excluding baseline	£ 187.25	SD: 169.33	£ 52.48	SD: 52.48

Table 20 Notes: Data include all patients that responded to questions on prescribed medication in the trial. 1 patient in the Intervention Group and 7 patients in the Control Group reported drug costs at Baseline. 5 patients in the Intervention Group and 10 patients in the Control Group reported drug costs at Week 6. 8 patients in the Intervention Group

Patient costs

Information on out of pocket expenses was collected in the questionnaires. Participants were asked if they had bought medicines or other equipment related to their condition at every follow up. They did report out of pocket expenses for medicines and the majority of patients who responded reported costs related to their NBD needs. The most common items reported were laxatives, suppositories and continence pads. The out of pocket expenses for incontinence pads and other items are summarised in Table 21. In terms of average out of pocket cost per participant, there is a very small difference between the two groups and the higher spending costs seen in the Control Group were driven by one individual only. We only report total costs for the two arms and a mean cost by dividing by the number of patients who reported in each group here. Overall, out-of-pocket reported spending per patient was very small in both groups and again due to the low numbers that responded to these questions we do not take into account these costs in the cost-effectiveness analysis that follows.

Table 21. Total reported patient out-of-pocket costs (£) by trial group

	Intervention Group (£)	**Control Group (£)**
Out-of-pocket costs from Baseline to Week 6	£244.96	£409.98
Out-of-pocket costs from Week 6 to Week 24	£148.93	£541.10
Total Out-of-pocket costs	£393.89	£ 951.08
Mean out-of-pocket costs per patient through to Week 24	£6.57	£11.46

Table 21 Notes: Data include all patients that responded to these questions. 5 patients responded in the Intervention Group and 11 patients in the Control Group at Baseline. 6 patients responded in the Intervention Group and 4 patients in the Control Group at Week 6. 5 patients responded in the Intervention Group and 19 patients in the Control Group at Week 24. Total costs include all reported out-of-pocket costs.

EQ-5D-5L data

EQ-5D-5L data were collected via participant-completed questionnaires at Baseline, Week 6 and Week 24. The EQ-5D-5L responses were given in the two sections of the EQ-5D-5L questionnaire, the EQ-VAS and the EQ-5D Descriptive System.[40] The EQ-5D-5L descriptive system was scored using the UK tariffs.[41] Table 4 in Chapter 3 provides a summary of the EQ-VAS and EQ-5D Descriptive System index score. Higher scores represent better quality of life. In the cost-effectiveness analysis that follows we combine HR-QoL as measured by the EQ-5D-5L index scores in Table 4 with resource use costs as shown in Appendix 10 and intervention costs which were described previously and calculated to £90 and assigned to each patient in the intervention group.

Economic evaluation of abdominal massage (intervention) versus standard care (control)

The raw data indicate there is little difference between the two groups in this trial both in HR-QoL outcomes and costs. However, there was less QoL data to analyse than the number of recorded participant withdrawals or lost to follow up. Missing data occur frequently in randomised control trials as patients may withdraw, questionnaires may be unreturned and responses to individual questionnaire items may be impossible to use. In the AMBER study, one of the reasons for the differing numbers was the fact that in some instances when missing outcome data were chased, participants had said they had already completed the outcomes and returned in the post but this was never received (previously discussed in Chapter 3).

At the end of the trial, 58 patients in the Intervention Group and 83 patients in the Control Group had EQ-5D-5L data to analyse. To account for the missing data, and the highly imbalanced nature of the two groups that resulted in more missing values in the intervention group, the following statistical approaches[42] were followed: EQ-5D-5L data were analysed (Table 22) and then multiple imputation was performed. The imputed datasets were then bootstrapped to perform cost effectiveness analysis including NHS resource use costs and

interventions costs. In the economic evaluation that follows NHS resource use included all costs related to both bowel reasons and other health reasons as reported in Appendix 9. The results in Table 22 are not adjusted for missing values. The economic analysis of AMBER data employed methods described in another study to handle missing data by multiple imputation (to reduce bias and to make sure missing data is handled appropriately).[43] The economic evaluation, therefore, also included participants with only partial data. For the cost-effectiveness analysis, QALYs and total patient costs were calculated for the 6 months that the trial lasted. The imputation was run 60 times resulting in 60 different datasets to be used in the cost-effectiveness analysis. The imputation was implemented separately for the Intervention and Control Groups to account for differences in the missing values between the two groups.

Table 22. EQ-5D-5L Index scores and effect size

	Intervention			Control			Effect size (95% CI)*	
EQ-5D-5L Index scores	**Baseline N=90**	**Week 6 N=60**	**Week 24 N=58**	**Baseline N=99**	**Week 6 N=84**	**Week 24 N=83**	**Week 6**	**Week 24**
Mean (SD)	0.545 (0.246)	0.520 (0.290)	0.536 (0.276)	0.498 (0.281)	0.481 (0.271)	0.458 (0.277)	0.004 (-.061 —.068)	0.017 (-.047 — .081)
Median (Range)	0.615 (-.183-1)	0.570 (-.245-1)	0.592 (-.245-1)	0.555 (-.467-1)	0.527 (-.213-1)	0.548 (-.130-1)	p-value 0.916	p-value 0.605
*Adjusted for Centre, sex, disability and baseline. Bootstrapped 100 times								

Multiple imputation was performed using predictive mean matching.[44] The multiple imputation model uses baseline covariates (EQ-5D Index Scores, age, sex, duration of MS and severity of MS symptoms), costs and QALYs at each follow-up to impute unobserved costs and QALYs, so that, for example, missing costs at week 24 are imputed using data on baseline covariates, costs at baseline and Week 6 (if available) and QALYs between Baseline and Week 6 (if available). QALYs were imputed using EQ-5D index scores. One thousand bootstrap samples were drawn from each of the 60 multiply imputed datasets were analysed and the difference in net benefit between the treatment groups in each bootstrap sample was estimated (at a given threshold for cost per QALY). The proportion of bootstrap samples in which the net benefit is positive represents the probability that the

treatment is cost effective for each multiply imputed dataset. This probability is then averaged across all multiply imputed datasets.

Tables 23 and 24 show resource use spending at 24 weeks before and after imputation. As expected resource use remains not statistically significantly different between the two groups after imputation. Table 25 shows the estimates of costs and QALYs per patient in the multiple imputation models. These costs include intervention costs and resource use costs as shown in Table 25. QALYs were calculated from EQ-5D index score taking into account the trial only lasted 6 months.

Table 23. Resource use NHS costs per patient by trial group excluding baseline

	Intervention Group (£)	**Control Group (£)**
Mean cost per patient	416.40	487.01
Standard Error	130.70	83.84
Standard Deviation	986.79	768.39
95% Conf. Interval	[154.57-678.23]	[320.26-653.76]
t-test on the equality of means	$\|t\| = 0.47$	

Table 23 Notes: Data include all patients that participated in the trial. There were 58 patients in the Treatment Group and 83 patients in the Control Group at Week 24. Reported contact with NHS services from baseline to 24 weeks.

Table 24. Resource use NHS costs per patient by trial group excluding baseline after imputation

	Intervention Group (£)	**Control Group (£)**
Mean cost per patient	427.49	500.46
Standard Error	83.79	71.42
Standard Deviation	794.87	710.64
95% Conf. Interval	[261.01-593.98]	[358.72-642.19]
t-test on the equality of means	$\|t\| = 0.67$	

Table 24 Notes: Data include all patients that participated in the trial. There were 90 patients in the Intervention Group and 99 patients in the Control Group at Baseline. Reported contact with NHS services from baseline to 24 weeks after imputation. Average resource use costs from 60 imputed samples. See Table 31 for NHS services included in these calculations.

Table 25. Multiple Imputation Estimates

	Intervention Group (£)	Control Group (£)
Mean Costs per patient	590.44	540.65
Standard Error	127.44	96.28
Mean QALYs per patient	0.230	0.216
Standard Error	0.015	0.012

Table 25 Notes: Data include all patients that participated in the trial. There were 90 patients in the Intervention Group and 99 patients in the Control Group. Costs exclude baseline and include resource use NHS costs and intervention costs where applicable.

Table 26 shows the average incremental costs and QALYs for every patient obtained from the multiple imputed sample and the bootstrapping. The incremental cost effective ratio based on these data is negative at -£24,149 because the model estimates a negative incremental QALY.

Table 26. Mean incremental costs and QALYs per patient

			Confidence Interval	
	Estimate	**SE**	**lower**	**upper**
QALYs	-.002	.009	-.029	.027
Costs	56.50	116.99	-372.62	415.68

This method accounts for the uncertainty around the mean estimates of both costs and QALYs and to make conclusions about the cost effectiveness of abdominal massage compared to control, the probability of cost effectiveness at the £20,000 threshold of willingness to pay per QALY is calculated at 31.3%. That probability increases to 34.2% for a £30,000 threshold of willingness to pay.

To test if the results were affected by the imputation or the bootstrapping processes, two extra models were estimated. First, it was estimated that a seemingly unrelated regression model was applied on the imputed datasets.[45] Secondly, a mixed model was employed using maximum likelihood estimation.[46, 47] The mixed model did not require an imputation step, this approach is a good check to see if imputation affected the results. The results of the seemingly unrelated regression model and the mixed model are shown in Appendix 11.

These results are similar to the bootstrapping model and all three methods predict a probability of cost-effectiveness that is lower than 50% at the £20,000 threshold per QALY gained. Both imputation models predict a negative QALY gain after controlling for baseline HR-QoL in these models. For this reason the ICER of these models is negative making straightforward comparisons rather difficult. The mixed-model also controlled for baseline HR-QoL but the estimate on incremental QALYs and the ICER of this model was positive. In all three estimated models the impact on quality of life is close to zero and with relatively large standard errors reflecting the uncertainty around patient utility scores. The mixed model point estimate of the ICER is at £28,722 which is over the £20,000 threshold.

In sensitivity testing we further controlled for patient characteristics (age, gender, duration of MS and severity of MS symptoms), along with baseline HR-QoL, in the three models but this did not significantly change our results. In another sensitivity test we varied unit costs by 20% but this did not have a significant impact on the probability of cost-effectiveness either due to similar resource use between the two groups. In a final sensitivity test we explored the impact changing the intervention cost. We run all three models with the intervention halved and doubled. The results do appear sensitive to the intervention cost as the probability of cost-effectiveness at the £20,000 threshold per QALY gained ranges from 21% for high intervention costs of £180 per patient to 55% probability of cost-effectiveness for low costs of £45 per patient. Notably, the point estimate of the incremental cost effectiveness ratio drops to between £6,000 and £7,000 which is in the cost-effective range given a threshold of £20,000 per QALY gained. As described earlier it is more likely that the intervention costs will be lower than £90 per patient than otherwise and the results in Appendix 11 should be considered as conservative. However, it should be noted that given the negative QALY increment, the control was bound to dominate as long as the mean cost was higher in the intervention group.

The economic evaluation results show that abdominal massage is less likely to be a cost-effective alternative to standard care than the other way round. However, all models predicted a probability of cost-effectiveness higher than 30% and in the mixed-model close to 47%. In sensitivity analysis this probability was higher than 55% assuming a low intervention cost per patient. The probability of cost-effectiveness can be seen as the probability that an individual (random) patient will have a positive individual incremental net benefit. It can also be seen as the proportion of all patients in the population who have positive individual incremental net benefits therefore it is reasonable to assume that our results suggest that there is a subset of patients who had a positive incremental net benefit from abdominal massage.[48] If there were

no patients with a positive net incremental benefit then the likelihood of cost-effectiveness would have been close to zero. Further research is needed to establish the type of patient that may have benefited for abdominal massage (discussed further in Chapter 6).

This economic evaluation has certain limitations. First, we excluded drug costs and out-of-pocket costs since very few participants responded to these questions. The patients who responded reported very low costs per patient and we do not expect that inclusion of these would have a large impact to our results. Second, we did not perform sub-group analysis by estimating these models on a sub-set of patients. We decided against that because regression results (available upon request) did not show a statistically significant impact of patient characteristics, such as age and gender, on costs and QALYs gained. Finally, we do not extrapolate our results over a longer horizon than 6 months. Our results suggest that the impact of the intervention on quality of life as measured by the EQ-5D-5L is small and we do not expect significant differences in the probability of cost-effectiveness if the trial lasted for a longer period.

CHAPTER 5 Process Evaluation

Introduction

The AMBER trial includes a process evaluation, in line with advice from MRC guidance for evaluating complex interventions[49-50]. This is informed by realist evaluation methodology, which goes beyond the evaluation question 'What works?' to: 'What works, for whom and in what context?'[51] The aim of this approach is to situate and explain outcomes within the contexts in which they are achieved in order to explain potential discrepancies between expected and observed outcome, and to assess fidelity to implementation processes. Furthermore, results of the process evaluation also provide data to inform the optimisation of the intervention and seek to explore potential routes to sustainable implementation. The process evaluation follows a longitudinal, case study design.[52-53]

The objectives of the process evaluation are thus:

- To explore fidelity to processes of implementation of the trial intervention
- To explore implementation contexts (including settings, demographics and implementation processes; delivery and take up of the intervention; adherence and non-completion)
- To explore intervention optimisation and sustainability beyond the life of the funded project.

The chapter presents the research methods for the process evaluation, the results of the analysis of data from interviews, bowel diaries and telephone support recordings. The chapter ends with practice recommendations.

Methods

Recruitment and Sampling

People with MS

A total of 20 PwMS taking part in the trial, and randomised to the Intervention Group, were selected via convenience sampling.[54] The small numbers recruited into the trial from each site meant that our intended purposive sampling strategy was not feasible. However, as Figure 1 illustrates, the sample achieved a variation in terms of geographical location, age, different types of multiple sclerosis and stage of disease progression. This sample variation

facilitated the exploration of hypothesised 'context, mechanism and outcome' (CMO) configurations. We did not adhere rigidly to definitions of 'contexts' or 'mechanisms,' since previous experience of using this approach informs us that contexts can become active mechanisms that promote change in some instances and, at other times, mechanisms of action can be better conceptualised as contexts.[55-56] For instance, sampling reflected the following hypotheses: that there could be gender differences in the acceptability of massage, severity of MS might have an impact on ability to do the massage, and length of time living with MS may also contribute to attitudes towards self-care. This sample is reflective of the characteristics of trial participants as a whole, with those aged over fifty years of age and females being the most prominent. The mean age for the Intervention Group of the trial was 53.5 (51.3 for those in the Control Group); 84.4% of intervention participants were female (78.8% for the Control Group). Sixteen of interview participants lived in the North of England, reflecting the fact that half of the 12 sites involved in the study were located in that part of the UK. Further considerations on patient characteristics are elaborated on under the data collection section. Table 27 provides further details on the characteristics of those interviewed.

Table 27. Characteristics of interviewed participants

Age range	**Gender**	**Employment Status**	**Geographical Location**	**Type of MS**	**Years with MS***
<21 n=0 21-30 n=0 31-40 n=1 41-50 n=4 51-60 n=7 >60 n=8	Male n=1 Female n= 19	Unemployed n=2 Employed n=3 Business owner n=1 Retired (on ill health basis) n=12 Retired (reached retirement age) n=2	W Scotland n= 3 NW England n=10 NE England n=6 SE England N=1	Benign N=0 Relapsing remitting n=11 Secondary Progressive N=8 Primary Progressive N=1	<5 n=3 5-10 n=3 11-20 n=6 21-30 n=3 >30 n=6

*This is estimated, since a number of patients reported living with MS symptoms for years

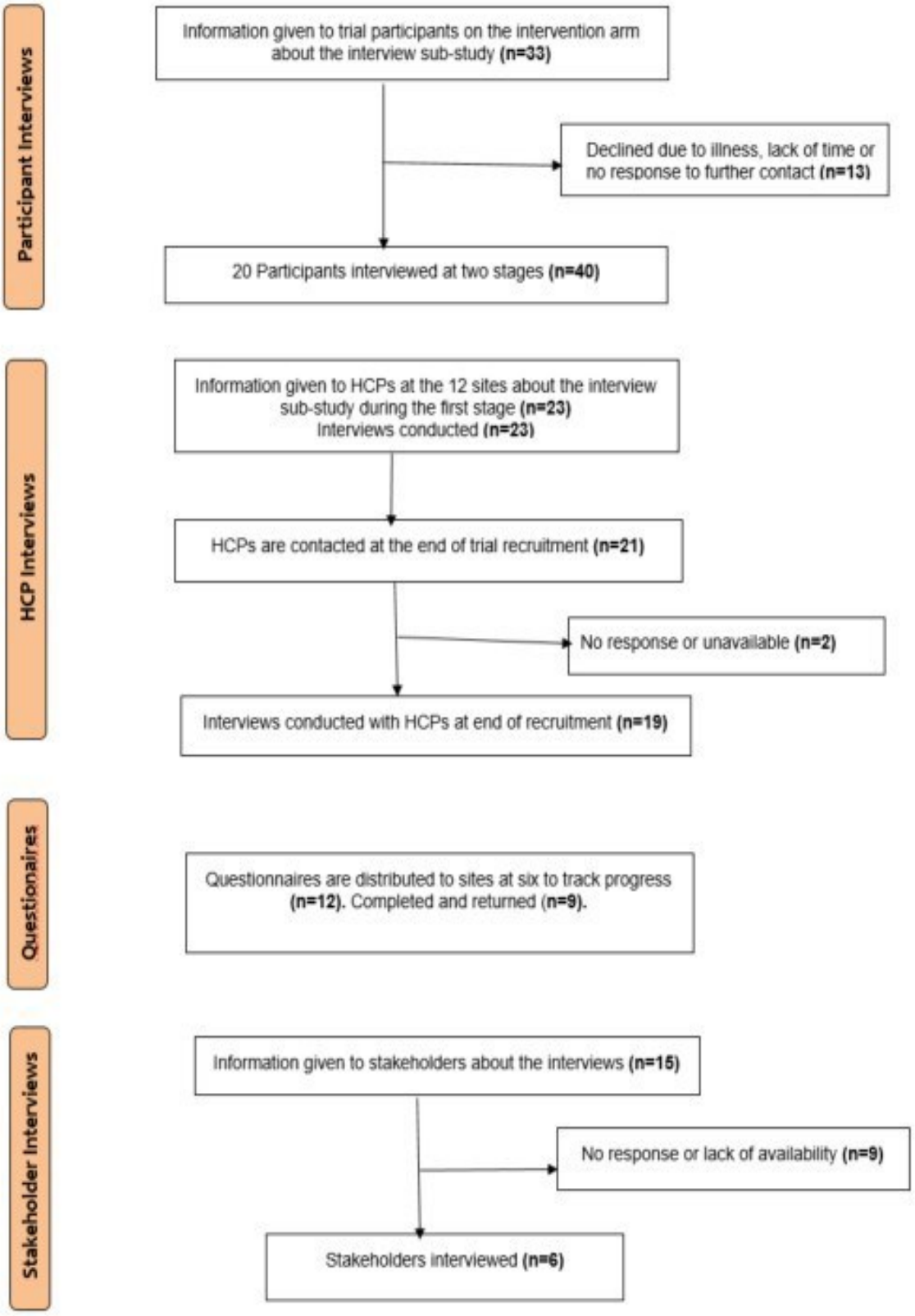

Figure 10 Flowchart for the Process Evaluation

By the time of the first interview, participants had been enrolled in the trial for around four weeks. All those who took part in a first interview agreed to participate in a second interview. A total of 20 PwMS were interviewed twice, giving a total of 40 interviews.

Healthcare Professionals

Forty-two interviews were conducted with 25 different healthcare professionals (HCPs). One to two people involved in delivering the AMBER trial from each of the twelve sites were recruited to interviews. The range of involvement in the trial varied from those who delivered the massage training and/or the participant follow-up to the local principal investigators whose role centred on identifying suitable patients for the trial. Appendix 12 documents the roles of HCPs interviewed and numbers of interviews. This sample was also designed to reflect the realist evaluation approach.

Initial interviews with HCPs were usually conducted within a few weeks of recruiting their first intervention participant. Due to variation in site initiation and trial recruitment, initial interviews took place between January 2015 and March 2016. Twenty-three staff members were interviewed during this first stage.

Second interviews were sought with staff members who were actively involved in patient training and follow-up in order to explore any problems that may have arisen since the first stage of interviewing. In a small number of cases, a different staff member who had since become more involved in the trial or delivery of the treatment was selected for interview at the second stage. Nineteen staff members were interviewed in the second stage of interviews.

Stakeholders

Six interviews were carried out with stakeholders purposefully selected for their expertise in neurological and incontinence treatment provision, policy-making and service development. The process of identifying suitable interviewees began with research into neurological and incontinence services throughout the United Kingdom. Snowball sampling was also used, where those interviewed recommended other potential interviewees. Appendix 12 illustrates the types of organisations and interviewees that were interviewed.

Fifteen potential interviewees were contacted and 6 people were interviewed after giving informed consent. The interviews took place from early to mid-2016, in order to capture

their knowledge and insights into recent policy and clinical developments related to the treatment of MS.

Data Collection

Interviews

The data collection consisted of qualitative semi-structured interviews, allowing the views and 'lived experiences' of participants to be explored.[57] Interviews drew on topic guides (see Appendix 13), taking an iterative approach to allow unanticipated themes to be explored in subsequent interviews.[57] All interviews were conducted via telephone in order to save on travel costs, as interviewees lived in locations throughout the United Kingdom.

The purpose of interviews with trial participants was to explore experiences of living with multiple sclerosis and bowel problems, as well as experiences of taking part in the trial. The second stage of interviews focused on exploring any change in symptoms, any adaptations to the massage they had made, further thoughts on taking part in the trial and whether they intended to continue abdominal massage at the end of the trial. Appendix 13 details the main topics covered in each stage of interviews and Appendix 14 the interview schedules and site questionnaires.

The aim of the interviews with HCPs was to explore issues of training processes (both their own training in massage as well as delivering massage training to trial participants), trial

delivery and implementation. The first stage of interviews aimed to detect any problems faced in delivering the trial and anything that worked well. The original interview transcripts were used to write the topic guide for the second stage of HCP interviewing. Second stage interviews gathered an overview of staff members' experiences in participant recruitment, the delivery of massage training and advice and participant follow-up. Appendix 13 gives an indication of the topics explored during both stages of interviews with HCPs.

Stakeholder interviews explored ways to implement the abdominal massage intervention on a larger scale and any potential challenges to doing so. Background research was conducted into the organisations interviewees worked for. Current neurological and incontinence policy developments at local, regional and national levels were also extensively researched to ensure that appropriate, targeted questions were asked during the interviews. Whilst wider policy developments and trends were acknowledged during interviews, the focus remained on those that may facilitate or hinder the possible implementation of abdominal massage treatment. Appendix 13 gives an indication of the range of topics covered in stakeholder interviews; although this varied given the expertise of each organisation and interviewee.

Data Analysis

Interview recordings were transcribed verbatim. Data were analysed drawing on an adapted framework approach.[58] This followed an initial categorising and coding process similar to thematic analysis, using the qualitative data analysis software QSR NVivo (v.10). Coding and all further stages of analysis were conducted by SD and checked for consistency by FH. Analysis was conducted continuously with interviewing, contributing to the iterative process, allowing emerging themes of interest to be explored further in future interviews. The initial coding was then transferred into framework matrices for the three categories of interviewees. These summary tables explored within-case issues, where each trial site was considered as a case, i.e. the unit for analysis. Analysis paid attention to any contextual differences that could have an impact on outcomes. Cross case comparison then identified higher level themes that explored facilitating contexts and mechanisms and any barriers to successful implementation. The matrices also tracked the process of change over time, taking account of the longitudinal aspect of interviews. Interviews with PwMS also retained attention to case study sites to ensure analyses were sensitive to any contextual variations. However, given the small numbers recruited from each site, we have not identified participants by

recruitment location. Identifiers in quotes simply read as e.g. PwMS 1 or HCP 1. Where second interviews were conducted with the same person, the identifier illustrates this by the additional number so that, for instance, the second interview with PwMS 1 would be identified as PwMS 1_2. Bowel diaries were also analysed for those participants who reported either no improvement or only a temporary improvement in bowel symptoms. To ensure validity and reliability of the analyses, these tables were deliberated within the process evaluation team (SD and FH), and received further clinical input from the wider study team.

Results

This section presents the analysis of interviews with trial participants alongside bowel diary analysis, and analysis of interviews with HCPs, and higher level stakeholders. The within case descriptive data informed the beginning of Chapter 5; here the focus is on presenting experiences of trial participation and a cross case comparison of implementation issues drawn from interviews with HCPs.

Bowel Dysfunction and Treatment

We begin this section by exploring the experiences of interviewees, who provided some powerful narratives of how living with neurogenic bowel dysfunction impacts on their everyday lives. This is followed by views from HCPs and Stakeholders on current treatments and the delivery of care for constipation.

Living with Bowel Dysfunction

Trial participants revealed the extent to which quality of life is impeded by severe constipation, which might range from passing a stool four times per week up to once a fortnight. Bowel problems, coupled with their impact on other symptoms, had a negative impact on the quality of their lives: *"My whole life is ruled by my bowels – that's all I think about every day 24/7*" (PwMS20_1). One person explained how they felt thus:

> *"I can go for days without having to go to the toilet, it can be like a week and of course my stomach ends up bloated away out to here and then you get worried that if you go out somewhere that you're going to have to make a quick dash to the toilet, and then when you're there you can be there for ages; so if you're out with friends and you disappear to the toilet, you're stressed cause you think, "God, they're going to wonder where I am, what's happened?" and it becomes embarrassing then, and I have on maybe two occasions actually had an accident when I've been out and it's just been an absolute nightmare, so you've got to try and plan ahead, you know, to work round it"* (PwMS11_1).

This sometimes resulted in taking extreme measures to cope with symptoms. For instance, some participants avoided eating at certain times because of the uncertainty of when they would next pass a stool.

> *"I can't eat because I'm scared, I can't eat because I don't know when I... if we're going on holiday I can't eat because I don't know when I can go to the toilet again or what the toilet facilities are when you go away and things like that. And when I went* [on holiday] […] *I only ate two of those six days and I managed even though I was really, really hungry"* (PwMS20_1).

Constipation was linked to laxative usage, which also could result in negative side-effects. Interviewees reported that taking laxatives caused pain, sleeplessness, cramps and diarrhoea. The unpredictability of passing a stool when taking laxatives meant a number of patients became very concerned about their potential for bowel accidents, sometimes not leaving home for days because of the lack of control. For some people, this can lead to social isolation.

> *"At the moment it's absolutely disastrous, like today I won't even answer the doorbell if the doorbell rings.* […] *That's what happens when I have a day that I know I'm going to spend it hanging around hovering trying to go to the toilet, I can't even answer the door, I can't leave the toilet cause I'm scared I'll have an accident,* […] *I have no control whatsoever"* (PwMS20_1).

Current Delivery of Care for Constipation

HCPs and stakeholder interviews revealed consistent views that abdominal massage could provide a useful addition to current treatments that commonly involve oral therapies. Abdominal massage has a number of positive attributes as a form of treatment: it is cheap, low-tech, simple, non-invasive, and can be used anywhere.

However, stakeholder interviews revealed that most patients are under-informed about bowel matters. They stated that people do not fully understand constipation; thus, in some cases, do not report it as an issue until it is quite advanced. Furthermore, HCPs reported that constipation is not discussed enough, and patients may not connect this to their MS. There is also a lack of evidence and education around treatment for bowel problems. Furthermore, the huge workloads of MS nurses have led to increasing numbers of MS patients being managed by general nurses (Stakeholder1; Stakeholder4). As one stakeholder put it: "*Excellence in*

continence care comes from a degree of specialists, who would be able to make better decisions and better treatment plans at a local level" (Stakeholder6).

Ten out of the 12 sites did not currently use abdominal massage as a form of treatment for bowel problems. Although 1 site had a bowel specialist who offered some form of abdominal massage, MS patients were only referred to her when their bowel problem was at a critical stage. The other site currently using abdominal massage offered specialist bowel clinics as part of a community service. This meant that this site struggled to find PwMS who had not used abdominal massage before to recruit into the trial. One further site had previously used abdominal massage as part of the continence service; however, only 1 member of staff had been trained in it and had since left, so massage treatment was no longer offered.

Experiencing and Delivering the Intervention

In this section we explore how the intervention was experienced by participants and also issues around implementation. Interviews gathered data on various aspects of trial experience and delivery that may inform any future implementation of abdominal massage as a treatment for PwMS. This included experiences of massage training, supporting materials and telephone support. This is reported below in brief.

Recruitment and Retention

By the end of recruitment four sites had recruited to or exceeded their targets. The main reasons for failing to meet recruitment targets centred on under-staffing and time constraints. At one site, this was entirely reliant on one research nurse, who was also working on 15 other trials. This meant she did not have the time to repeatedly chase patients and was sometimes not available to see them in clinic. The incorporation of the AMBER trial into the existing workloads of staff members also proved troublesome in some cases, with an already limited staff capacity further stretched unexpectedly by sickness absence or resignations.

Sites that did not meet their recruitment targets were nevertheless usually successful in retaining those that were enrolled on the trial. Retention was affected by being patient-centred in approach during baseline appointments. In the case of one site, both staff members involved attended every baseline appointment: one demonstrated the massage technique;

whilst the other checked the paperwork. These were also all home visits, since that was more convenient for the patients. Another site that conducted home visits reported the unexpected benefit of establishing a better understanding of patients' home contexts: "*It helped to see them at home because you had an idea about their home set-up – how chaotic their lives were*" (HCP19_2).

Probably the most important contributor to retention was the relationships established between those delivering the trial and the participants. For some sites, this was facilitated by the fact that patients already knew the staff members involved. One way of enhancing the rapport with patients was to have the same staff member carrying out the weekly calls: "*I think it's just getting to know me and feeling comfortable with giving me information*" (HCP21_2). Being supportive and offering advice during the first appointment and follow-up also appeared to enhance retention.

Massage Training

Delivery of massage training by HCPs

The massage training delivered to participants during the baseline appointment was a critical component of the trial. Staff members had a variety of techniques: showing participants how to position their hands during the massage; administering the technique on them to give them an idea about pressure; watching participants do the massage themselves and commenting on it. A problem that arose was that during this initial training, some people preferred the massage to be administered over their clothes or on body parts other than their stomach. This may have affected how the staff member was able to deliver that training, since the massage should be administered on the abdomen in order to allow them to gauge pressure. As per the AMBER protocol, they advised that a carer or spouse could administer or assist with the massage or they could use their fist as opposed to a flat hand in order to provide more pressure.

Trial participants

All 20 trial participants agreed that the massage training and follow-up materials were very useful. For most participants the training involved being given the AMBER DVD, having the massage demonstrated on them and then engaging in supervised practice. A quarter of interviewees had their partner present at the baseline appointment to also receive the training:

"If there's a day where I'm not capable of doing it or can't remember a bit, then I'm covered" (PwMS3_1).

Most interviewees were very positive about the massage video: "*The DVD is brilliant. It is so simple and easy to understand*" (PwMS12_1). Engagement with the DVD was enhanced by the woman demonstrating the massage in the video, who appeared to normalise the technique: *"She's a real person…when I saw her I immediately relaxed and felt I could do it"* (PwMS3_1). Feedback on the video was positive, and after initial viewings, most people used the quick reference guides as aids during the administration of the massage. The quick reference guides were found to be helpful, clear and portable, and ideal to use whilst administering the massage. The few negative comments about the DVD were related to the format, as some participants found that their copy of the DVD would not work on their DVD players and had to seek alternative copies. Others preferred to use the information leaflet as it was easier to carry around and refer to.

Experiences of doing the massage

The frequency of administering the massage varied and participants fitted the massage around their daily routines. A number stated a preference for last thing at night as part of their bedtime routine: "*It's part of my ritual now, before I go to bed"* (PwMS15_2). However, all participants adjusted the frequency and timing of their massage routine based on their stamina levels and personal circumstances. Circumstances that interfered with the massage routine included: grandchildren visiting, a house refurbishment, family bereavement and festive periods such as Christmas. Health problems that affected adherence included diarrhoea, vomiting and bladder infections.

Physical weakness and numbness in fingers, hands and arms caused by the MS posed another challenge and this led to several participants adapting the massage technique to suit their abilities or enlisting the help of a partner. Adaptations included: administering the massage first thing in the morning (when feeling stronger) and using one hand to guide the other; asking a partner to assist with parts of or the whole massage routine.

As Table 28 illustrates, we drew on these results in order to establish some key 'context-mechanism-outcome' (CMO) configurations that might impede or facilitate positive impacts. Those contextual factors that might facilitate positive outcomes are linked to the adaptability

of participants, with those who demonstrate an ability to adapt either the massage techniques or massage oil to suit their own capabilities and preferences.

Table 28. Context-mechanism-outcome Configuration: Adaptability and capability

Context	Mechanism/Action	Outcome
Severity of MS	Ability to do massage	Impedes adherence or effective massage technique unless administered by a carer
Physical weakness/mobility issues/fatigue	Adaptability and commitment to continue	Achieves adherence via adaptations to massage technique or enlisting help
Greasy massage oil leads to increased time involved (e.g. showering after massage); may reduce adherence	Adaptability and commitment to continue – use alternative massage products	Continued adherence; no lubricant used may lead to poor massage technique and negative outcomes

Supporting and experiencing the trial

Site staff made weekly calls to participants in both the Intervention and Control Groups for a period of 6 weeks and then again at the 24-week stage. Fourteen of these calls were audio-recorded from eight of the twelve sites in order to check fidelity to the AMBER support call protocol. Calls were not recorded at the remaining sites due to the timing of patient calls, the site not completing the calls (the AMBER trial office took over this task for one site) and the availability of the recording equipment. In the sample of recorded calls, one was a Week 24; the remainder took place in Weeks one through to Week 6. The support calls were structured by a case report form (CRF) guide of questions and, at the 24-week stage, also asked about issues relating to the primary outcome measure. Questions covered the following three areas:

- Participant experience: changes to bowel habits, health condition and personal circumstances; self-administration of the massage (if applicable).
- Managing symptoms: usage of medication and laxatives; any changes to diet, fluid, exercise and positioning on the toilet seat.

- Delivery of the trial: more practical aspects such as time and staffing arrangements for weekly calls and completing and returning paperwork.

From the 18 recordings, however, we were able to identify that in some instances these were not as supportive in discussing the lifestyle changes and/or the massage as we had anticipated and were more of a tick box exercise. In an effort to improve the quality of support, the Control and Intervention participant calls completed by one site which were deemed by the AMBER trial office to be exemplary were transcribed, anonymised and circulated to all sites as a good practice guide.

Further review of these transcripts highlights a number of strategies that may have enhanced participant engagement in the trial. Some HCPs referred to the results from the previous call or information in participants' forms, highlighting the value of providing information about their condition. Callers gave positive reinforcement to encourage positive lifestyle change, explored diet and fluid intake and advised on massage technique. Some of the callers reminded participants to complete and return paperwork and advised on how to complete the questionnaire.

The weekly telephone calls from sites were positively received by participants. The additional support available from staff members seemed to be the main attraction, as one person stated, "*It's nice to think there's somebody out there that's listening and helping*" (PwMS2_1). Participants found the advice useful and supportive and this may have been one of the reasons that trial retention was high within the Control Group. The only minor points of criticism came from a few trial participants who became anxious over missed calls and one person was initially given the wrong dates, which led to waiting in for calls that never came: "*We had a wee bit of a hiccup with the first one, I was sitting waiting because it was written down as the 19th and it was written down as a Monday and I remember her saying about a Monday and I sat for about an hour and nobody phoned"* (PwMS13_1). However, this initial mix up with dates was sorted out and subsequent calls were received when expected.

Participants' reactions to the trial paperwork were mixed. While some participants found the paperwork tiring and burdensome, a number of people felt that completing the bowel diary was invaluable for keeping track of progress and may have encouraged adherence to the massage: "*You forget and think 'did I go or did I not go?' and then you have a look back and you're like 'oh, yeah, I did"*" (PwMS9_1). During the second stage of interviews, some

people said they would have liked to have continued completing the bowel diaries, as this acted as a record.

The general consensus from HCPs was that paperwork was fairly straightforward for participants to complete, with the exception of one person who had severe visual impairment. In this case a staff member completed the paperwork during the baseline appointment and the participant developed their own bowel diary. This issue may have been mitigated by large print materials for visually impaired participants.

A number of suggestions were made by HCPs to improve the bowel diaries. These included being more explicit about when they should be started and picking up an error in stool frequency, which added up to more than 100%. It was also reported that bowel diaries did not fully capture bowel habits: for instance, although it recorded number of attempts to pass a stool, it did not record how many times this led to a bowel movement. Another area of confusion was the options for laxative usage of 'usual,' 'less' and 'more,' and the lack of a category for no laxatives.

For whom does abdominal massage work?

Positive improvements related to massage

Three-quarters of those interviewed (n=15) reported improvements in their bowels as a result of the massage. The main benefit seemed to be a feeling of empowerment and control over their bowel habits: "*I know when I get to the toilet I'm going to have a bowel movement*" (PwMS17_1). By the time of the second stage interviews, one participant said: "*I have to make myself look back to see how bad things were because there's a terrific improvement"* (PwMS1_2). This was the case for many people in the second stage of interviewing, with them passing the 'ideal types' of stools (3 or 4) more frequently, and with less pain. For example, one participant who mainly passed stool types 1 or 2 every 3 to 4 days or more prior to the trial stated: "*It was just awful. I'd sit on the toilet for ages and ages and ages just knowing that I had to do something and it was painful*" (PwMS17_2). However, by the second interview, she had a bowel movement of stool type 3 or 4 every day. Others reported being able to stop taking laxatives and increased frequency of bowel movements or, as one person reported, the time spent trying to pass a stool changed from 3 hours to only 5 minutes.

While improvements were not so dramatic for others, nevertheless one of the consequences of even small improvements was, for instance, a reduction in anxiety about potential impaction and hospitalisation. Notably, when participants stopped doing the massage because of personal circumstances, any improvements in symptoms were lost: "*In some ways that was a positive thing because it proves that while I wasn't doing it* [the massage] *things deteriorated*" (PwMS3_2).

Other reported benefits from doing the massage included feeling less bloated, clothing becoming looser and a decrease in sluggishness, which reduced fatigue levels. As one person reported, "*I don't think I've been tired since I've been on this* [trial]" (PwMS14_1). Some participants were also able to stop or reduce laxative usage, which were reported to disrupt sleep patterns. Improved diet was also noted by some participants, which was particularly important for those who ate very little because of their bowel problems. One person, who had a diminished appetite at the beginning of the trial stated that by the end: "*It's weird to say I feel hungry, even saying the word starving"* (PwMS12_1). At the second stage of interviews all 15 people who had reported some improvements agreed that participating in the trial had been worthwhile.

Exploring reasons for no improvement

Five interviewees reported no improvement from the massage. A complete set of bowel diaries for these participants were analysed alongside their interview data in order to determine whether this captured any changes in bowel habits and to explore potential explanations for the lack of improvement.

A higher severity of MS and body numbness may well have interfered with the ability to administer the massage effectively. Indeed, one stakeholder interviewee reported that effectiveness of abdominal massage is likely to vary: "*Some people find it beneficial and some people don't find it that effective. I think it depends on how advanced the MS is*" (Stakeholder3). Furthermore, when delivering the massage training, one HCP expressed doubts as to the likely effectiveness of the massage due to reduced physical dexterity of some participants: "*Some of them when you're watching them doing it and you're thinking 'how effective is that going to be*?'" (HCP19_2).

Another person who found no improvement experienced a worsening of their MS during the course of the trial, perhaps impeding the potential to show improvements. Although bowel diary data support the reported lack of improvement, the interview data reveals that in fact

this person, unlike prior to the massage, now had sensation and was able to feel the urge to pass a stool. This was perceived as a positive change related to the massage that nevertheless would not have been captured by trial outcome measures. However, unfortunately this person's condition worsened during the course of the trial and reported the impact of worsening symptoms thus: "*I find now I've sort of got quite a bit worse and I find if I get down and do these massages I can't get up again, I have real trouble getting up. So I've had to stop doing them which was a shame really*" (PwMS5_2).

Two further participants showed no improvement on the main indicators for constipation and consistently responded 'no' to the question 'Do you feel you have emptied your bowel?' However, both of these participants reported 'ideal stool types' at baseline, indicating that the severity of constipation was not significant enough to demonstrate any improvement.

Another participant felt that although the treatment worked initially, this effect was not sustained: "*It started to work a little bit —that was really good —unfortunately it didn't last*" (PwMS16_2). The initial benefit was improved control over when bowel movements happened, which in her case meant that she no longer remained at home for three days at a time in fear of bowel accidents. Her bowel diaries reveal that she only ever passed type 1 stools and there was no noticeable improvement in frequency, stool type or amount of time spent passing stool throughout the course of the trial. As this participant was wheelchair bound, mobility issues may well have played a part in her ability to effectively administer the massage.

Despite a perceived lack of impact, these five participants remained in the trial. This may be due to their overall trial experience being positive. Indeed, perhaps a 'positive outlook' could explain why three of these participants expressed the intention to continue with the massage after the trial in case it did eventually work.

A coding matrix was applied to all interview transcripts from trial participants to explore attributes such as severity of MS, severity of constipation and massage adherence. This revealed contextual factors that affected outcomes, as illustrated in Table 50.

Table 29. Contextualising participant outcomes

Context	Mechanism/Impact	Outcome
High severity of MS: reduced mobility, fatigue, severe constipation, numbness and lack of sensation	Reduced ability to massage effectively or apply correct pressure unless carer administers the massage; high severity of bowel problem means it is difficult to show an improvement	No improvement (n=5)
Bowel diary reports show ideal stool type, reasonable frequency and duration on toilet	Bowel diary cannot demonstrate improvement as baseline recorded as 'ideal' with no capacity to demonstrate benefit	

Further analysis was undertaken to explore whether expectations of the trial might have been linked to perceived impact, as a means of exploring whether 'hopefulness' might have an association with subsequent outcomes. The majority of those interviewed had no previous knowledge about abdominal massage and were unsure of what to expect. As a result of this, around two-thirds of participants initially felt doubt about whether the massage would help them. This was especially true for those for whom other forms of treatment had failed: "*Because nothing else had worked like the Senna tablets and stuff, I was a bit like 'well, I wonder if it is going to work?*'(PwMS15_2). While frequency data must be approached with extreme caution when reporting on such a small sample, nevertheless Table 51 serves to illustrate the likelihood that there was no association between expectations and trial outcomes.

Table 30. Participant expectations and trial outcomes

Hopeful of improvement			**n**
Positive impact	**No impact**	**Positive impact**	**No impact**
6	2	9	3

Contextualising the Trial Primary Outcome

One further piece of analysis was conducted in order to explore the discrepancy between the statistical analysis of the Neurogenic Bowel Dysfunction (NBD) total score and self-reported outcomes of the trial. The NBD Total score for all interviewees were matched up with data from interviews. Table 52 illustrates the discrepancies found by comparing this data. While 15 interviewees reported some improvements related to the massage, only 7 participants recorded an improved NBD score between baseline and Week 24, 6 people showed no change and 7 worsened over the course of the trial. However, of those 7 who showed improved NBD scores, 2 of these interviewees self-reported as having not experienced any improvement in their symptoms. There are several potential explanations for these discrepancies. Firstly, both interviews and NBD questionnaires captured snapshots of participant experience tied into particular weeks. While interviews roughly followed the same time point as the trial measures, they were within the same month rather than completed at the same time as the trial measures. Secondly, and perhaps more importantly, the NBD questionnaire did not necessarily explore those aspects of participant experience that affected quality of life more generally, thus the discrepancy between self-reported outcomes and those measured by the NBD questions.

Table 31. NBD Scores Compared To Self-Reported Outcomes

ID	Type of MS	NBD Total Score	Adherence to massage reported in interviews	Perceived Impact
PwMS6	Relapsing-Remitting	Baseline n=13 Week 6 n=7 Week 24 n=88	Mixed. Some weeks this was daily; other times no massage.	No perceived impact. Continuing to take laxatives. Bowel diary shows ideal stool type and frequency of 3-4 stools per week.
PwMS16	Relapsing-Remitting MS	Baseline 6 6wk13 24wk9	Daily for 18 weeks then stopped.	No perceived impact. It initially worked and then no positive changes. Began taking opiates that affected appetite; has poor mobility and bowel diary shows lack of improvement.
PwMS18	Secondary-Progressive	Baseline 5 6wk5 24wk5	Sporadic. A few times a week up to week 6.	No perceived improvement. On medication for bladder problems; bowel diary shows ideal stool, regular frequency but not feeling full evacuation.
PwMS20	Secondary-Progressive	Baseline 12 6wk21 24wk24	Daily.	No perceived improvement. High severity of MS and body numbness means massage likely not to be effective; does not seek help with massage.
PwMS5	Secondary-Progressive	Baseline 3 24wk3	Sporadic. Had problems with the massage oil and administering	No perceived improvement but now has urge to pass and feels gas moving after massage. Started taking an oral solution to treat constipation and feels

ID	Type of MS	NBD Total Score	Adherence to massage reported in interviews	Perceived Impact
			the massage.	that has worked. MS worsened during trial.
PwMS8	Secondary-Progressive	Baseline 14 6wk19 24wk13	Two to 3 times a week.	Slight improvement. It still takes a long time to pass a stool but massage seems to help and she has reduced stomach pain.
PwMS1	Primary-Progressive	Baseline 16 6wk 8 24wk 2	Daily (carer assistance)	Improved: passing a stool daily. Decreased laxative usage. Better sleep
PwMS2	Secondary-Progressive	Baseline 1 24wk 8	Two to 3 times a day.	Improved: stools feel more solid. Bowels are 'functioning better.' Improved appetite. Longer on toilet but greater emptying.
PwMS3	Relapsing-Remitting	Baseline 7 6wk7 24wk7	Five times a week.	Improved. Passes a stool every two to three days with 'less bother.' When stopped massage improvements disappeared.
PwMS4	Relapsing-Remitting	Baseline 1 6wk6	Daily.	Improved. Passes a stool every two to three days and she has managed to stop taking laxatives. Improved appetite.
PwMS7	Relapsing-Remitting	Baseline 5 6wk6 24wk5	Daily.	Improved. Feels if she starts to feel constipation the massage clears it. Managed to stop taking oral constipation solution.

ID	Type of MS	NBD Total Score	Adherence to massage reported in interviews	Perceived Impact
PwMS9	Relapsing-Remitting	Baseline 5 24wk3	Every second day.	Improved. Passes stool three times a week and has stopped taking laxatives. Without massage there is no movement at all.
PwMS10	Secondary-Progressive	Baseline 5 6wk11 24wk3	Daily.	Improved. Passes stool every second day. Greater sensation of emptying, less bloating, improved appetite and energy levels.
PwMS11	Relapsing-Remitting	Baseline 3 6wk11 24wk8	Daily.	Improved. Feels it is easier to pass a stool.
PwMS12	Relapsing-Remitting	Baseline 11 6wk13 24wk11	Daily.	Improved. Passes a stool daily and it is the ideal type. Improved appetite, less bloating and reduced abdominal pain.
PwMS13	Secondary-Progressive	Baseline 21 6wk13 24wk8	Five times a week.	Improved. Passes a stool once a week with more ease and it takes less time (reduced from 3 hours to 5 minutes). Has lost weight since being on the trial (regarded as positive).
PwMS14	Relapsing-Remitting	Baseline 11 6wk7 24wk14	Every second day.	Improved. Passes a stool three to 4 times a week. Stopped massage during trial due to bladder infections but plans to resume as felt that it worked.

ID	Type of MS	NBD Total Score	Adherence to massage reported in interviews	Perceived Impact
PwMS15	Secondary-Progressive	Baseline 3 6wk11 24wk7	Daily.	Improved. Passes a stool four times a week with less pain. Stopping laxatives. Less bloating and feels full evacuation.
PwMS17	Relapsing-Remitting MS	Baseline 7 6wk0 24wk4	Three times a week.	Improved. Passes a stool every day with more ease and stopped laxatives. Feels lighter.
PwMS19	Relapsing-Remitting	Baseline 7 24wk14	Daily (carer-led massage).	Improved. Passes a stool every six days and has reduced abdominal pain, less bloating.

Post-Trial Intentions

From discussions with participants during second stage interviews, it appears that all but two of them intended to continue with the massage. This is either because it worked for them or they hope that it will work in future. The massage seemed to have been incorporated seamlessly into their routines.

Views on Potential Future Implementation

This section explores the views of both HCPs and Stakeholders regarding the potential to implement the intervention within the NHS. This data is situated within the larger body of work conducted by the process evaluation team and interviews were done on the premise that the intervention **may** demonstrate effectiveness and was carried out before the results of the trial were known.

HCPs in the majority of sites reported issues related to staff capacity, which represents a potential barrier to future implementation of abdominal self-massage within the NHS.

Across all services in NHS England and Scotland, there are threats to the specialist nurse role and other positions through de-specialisation, redundancy and not replacing staff members when they leave. At one site, there was a problem with staff recruitment and retention, which resulted in a reliance on agency staff to deliver the service.

In order to successfully implement abdominal massage as a form of treatment, staff members would require reassurance regarding workload and capacity. There was a perception that this would require additional resource, although in many cases this might replace more invasive, time consuming treatments and could reduce the 'revolving door' of hospital admission or attendance for severe constipation. There were also concerns that if massage training were extended to other patient groups, there could be a resulting marked increase in referrals: "*We could potentially be inundated with patients*" (HCP16_2).

There was also some debate about which staff members would be best placed to deliver the massage training. It was suggested that massage training could be offered by the colorectal and continence team in hospitals or built into existing MS or continence clinics. This could be coupled with the DVD and written training materials to assist people in learning the technique. Furthermore, it was suggested that the massage could possibly benefit patients on bed rest or in nursing homes: "*That could be something we teach them to look after more progressive patients*" (HCP18_2). It was suggested by some sites that community and district nurses could become involved in training people in massage in their homes. Indeed, there were indications that abdominal massage could be introduced to a wider population in a range of healthcare and community settings.

Enthusiasm for abdominal massage was such that a number of sites indicated a willingness to incorporate it into current services. For instance, a HCP from one site that had set up a bowel clinic during the trial said that since the staff members who delivered the AMBER study were already trained in the massage, this could be rolled out more widely. Interest was also expressed in distributing training materials and engaging in additional training.

Stakeholders indicated that there are a number of policy and capacity issues affecting the potential for abdominal massage to be successfully implemented within the NHS. Evidence of clinical effectiveness is required in order to convince commissioners and other services to support this new treatment option. Moreover, in the current NHS environment, health boards and trusts are "*just looking for a short-term gain from cost savings*" (Stakeholder6), thus evidence of cost effectiveness is also important.

The case for abdominal massage needs to be persuasive in order to convince Clinical Commissioning Groups (CCGs), healthcare professionals and other services to adopt this

intervention if it was found to be effective. This might highlight, for instance, the potential for abdominal massage to free up capacity within GP, continence and MS services by dealing with bowel problems before they deteriorate (Stakeholder4; Stakeholder 5). Training in the massage could be framed as up-skilling staff members: "*It should be career-enhancing rather than career-threatening for those involved*" (Stakeholder 6). It could also reduce the costs and capacity issues associated with long-term bowel damage: unplanned hospital admissions, bed occupancy, and the prescribing of medications/other forms of treatment (Stakeholder 1; Stakeholder 2; Stakeholder 6). Secondly, there would be the potential to improve quality of life for patients: "*It's the cost to the patient of the indignity of having bowel management such as a suppository*" (Stakeholder 2).

A potential barrier to implementation is the challenge of "*getting something from best practice to common practice*" (Stakeholder 4). Firstly, massage treatment would likely be most useful if administered at an early stage in the development of constipation problems, rather than when patients are at crisis point (Stakeholder 3). GPs are integral to this process: "*They see the whole person and spot potential issues around bowel dysfunction at a much earlier stage*" (Stakeholder 6). A healthcare assessment for each individual needs to be carried out to determine what is causing the constipation and to ensure that abdominal massage is the right treatment for them (Stakeholder2). Furthermore, one stakeholder suggested that abdominal massage should be part of an individual's self-management programme, supplemented by advice around fluid intake, changes to diet and exercise suggestions (Stakeholder 5). The use of tracking tools like bowel diaries can help demonstrate how things have progressed (Stakeholder 2; Stakeholder 3).

Stakeholders felt that abdominal massage could be taught by community nurses or other HCPs such as general nurses, physiotherapists and continence advisors (Stakeholder3). They also suggested that consideration should be given to how this treatment could be taught to those who are severely disabled and unlikely to be able to self-massage (e.g. those in care homes). As reported by HCPs above, this suggests the need for staff members at care homes to be trained in the carer-led massage.

Stakeholder interviewees suggested ways of disseminating the massage training materials in order to reach the people who matter most: those with bowel dysfunction and HCPs dealing with these issues. . To that end, PwMS would need to be given access to videos and other training resources; whilst HCPs would need to be trained in the intervention and how to teach it. Stakeholders suggested that a number of key organisations should be included in

approaches to dissemination of training and, where appropriate, training materials could be hosted on their websites:

- NICE
- NHS England
- RCN
- Association for Continence Advice
- MS Society
- MS Trust
- Association of British Neurologists
- UK MS Nurse Association.

Process Evaluation Discussion

The experiences of PwMS provide powerful illustrations of how constipation can have a wide-ranging, negative affect on their everyday lives. Quality of life is severely impaired, to the extent where some people are afraid to leave their homes and may end up socially isolated, anxious and in pain. Interviews revealed the vicious cycle of symptoms, where the fatigue commonly associated with MS[59] is exacerbated by constipation: reducing food intake, disturbed sleep due to laxative use and so on. Despite the symptom burden, there are few evidence-based treatments available and the cost to the NHS of dealing with constipation is substantial.[60]

The findings from the process evaluation demonstrate the potential for abdominal massage to be adopted as a bowel management technique more widely within the NHS. While 75% of interviewees (n=15) experienced improvements in their symptoms, we were able to offer possible explanation for the lack of improvement in others. In some instances, it would be more appropriate to report that there were only *minor* improvements rather than none, but these minor improvements were not detectable via primary and secondary outcome measures in the main trial. It seemed that only the more dramatic improvements were able to be captured. The training focused on supporting patients to administer the massage themselves, and while the AMBER protocol did include the option for carer/partner administered massage, in fact this option may have been missed by those unaware at the outset that they did not have had the physical dexterity to perform the massage effectively.

Most of the sites involved in the trial were not currently using abdominal massage as a form of treatment and the general consensus from both HCPs and Stakeholders was that bowel

problems in MS patients had to be better managed. Our interviews revealed that most participants intended to continue with the massage demonstrating the acceptability of this non –invasive treatment.

The process evaluation presents results of an approach drawing on longitudinal interviews. Following both trial participants and trial delivery over time allowed us to track processes of change and to offer explanations for trial outcomes. The finer nuance achieved by bringing together interviewee experiences with bowel diary data offered insights which suggest that the outcomes may actually be more positive than the statistical analysis suggest. Furthermore, arguably AMBER achieved greater value by incorporating insights on trial processes. While being mindful of the need to protect trial equipoise, the process evaluation team worked closely with the trial team to establish a feedback loop to report anything that could be easily addressed without affecting the intervention itself. For instance, the time burden associated with compiling information packs was reported back to the trial team and they subsequently changed the format of recruitment packs to address this. This ensured that HCPs within the sites felt listened to and encouraged them to reflect on the trial and share their feedback with us.

Capacity issues at sites mainly affected recruitment levels in the trial. Under-staffing, part-time contracts and hectic workloads meant staff members were limited in the amount of time they could spend on the trial. As some sites were already offering massage, this also meant that there were few eligible participants to recruit. Interestingly, it was reported across all sites that participants randomised to the Control Group of the trial were disappointed; yet, the retention rate was higher in this group. This may be because the Control Group had a greater incentive to remain in the trial until the end, when they would be offered the opportunity to learn the massage technique. Control Group retention may also have been positively affected by the telephone support offered by site staff. This may also have contributed to fewer differences between intervention and Control Group outcomes, because site staff gave advice on medications as well as lifestyle.

What may be extrapolated from our process evaluation is that there is the potential for massage to improve the symptoms of NBD which may lead to reduced hospitalisations, reduced prescriptions, HCP time and improved quality of life for PwMS, which adheres to the outcome measures of policy documents. The main macro-level changes from the massage are said by interviewees to be freeing up staff capacity in the long-term and greater quality of life for people with MS. The argument would need to be made that the short-term

work and costs associated with implementing massage training would save money in the long-term.

HCP and stakeholder interviewees expressed interest in implementing abdominal massage longer-term. A number of sites were willing to adopt abdominal massage as a form of treatment and many of these interviewees felt that there was potential to roll this out to wider population groups, in a range of health and community settings. Finally, the words of our trial participants are worth repeating:

> *"It made a terrific difference, in fact I have to make myself look back to see how bad things were because there's a terrific improvement yes. It's made an awful lot of difference to me 'cause things were really bad to start with, but they're a lot better now* (PwMS1_2).

There are some strengths and limitations to the process evaluation. Strengths include the fact that although we were unable to purposively sample, nevertheless the convenience sample yielded a participant mix that reflected our initial hypotheses regarding time since diagnosis, severity of symptoms and gender. This enables us to capture robust data from which to explore potential variations in the experiences of trial participation (PwMS), trial delivery (HCPs) and to reflect on issues of potential future implementation and sustainability. The healthcare professional interviews all included at least one staff member involved in delivering the trial at each site. This allowed the researcher to identify any challenges around recruitment or other trial processes that could be fed back to the trial management team. Another strength was the longitudinal nature of the research thus facilitating scope for follow-up on any problems raised during the original interviews and exploration of the longer term impact of abdominal massage. This is a methodological innovation rarely accomplished within process evaluations and is a major strength of the AMBER trial. Similarly, interviewing healthcare professionals in two stages provided an opportunity to talk to additional staff members who had become involved in the trial later on, allowing for the exploration of contextual factors such as change in capacity over time that might have impacted negatively on trial delivery and implementation.

There are, however, some limitations to the process evaluation study. Due to limited resources, only those on the Intervention Group were recruited for interview, therefore we could not explore any contexts experienced by Control Group participants that might also have had an effect on outcomes. Another potential limitation was that those who agreed to be interviewed are likely to have a higher level of engagement with the trial; thus, they may be

both more likely to fully participate in the intervention and remain in the trial until its completion. However, our analysis of bowel diaries linked to interview participants revealed that they had variable levels of adherence to the massage although all interviewees remained in the trial; interviews with those that did withdraw would have been informative. Finally, participants' expectations of the trial were not associated with positive or negative outcomes, suggesting that our conclusions regarding their trial experiences and outcomes can be used to interpret wider trial outcomes. Since only twelve sites (hospitals in Scotland and England) were involved in the trial, and our stakeholder interview numbers were small, the results cannot be seen to be representative of healthcare services across the whole of the UK.

CHAPTER 6 Discussion

Bowel dysfunction in people with Multiple Sclerosis has a significant impact on quality of life as demonstrated by this quote:

"My whole life is ruled by my bowels – that's all I think about every day 24/7" (PwMS20).

Despite this, it remains a topic that is often not discussed by patient or clinician and is perceived as an area with few evidence based treatment options.[17]

This is the first large randomised controlled trial looking at the short and long-term effects of a supported programme of advice on lifestyle intervention and training in abdominal massage compared to lifestyle advice. Moreover, this research adds to the evidence on the impact of neurogenic bowel dysfunction on quality of life, identifies the most frequent symptoms and possible mechanisms; it also facilitates the triangulation of the information from the quantitative and process evaluations sub-studies.

Overall, the study recruited to statistical target sample size the overall 20% drop-out being in alignment with that expected in our sample size calculation. The increment in the Primary Outcome Measure, the Neurogenic Bowel Dysfunction Score[32], favoured the intervention group but was small and did not show a statistically significantly different change between groups at any time point but we believe that findings of trials should not be described as 'negative' on the simplistic metric of whether the P-valu is strictly less than 0.05. There is a small effect (-1.64 units) which is around 2/5ths of the specified minimally important clinical difference (MCID, 4.21 as specified in the power calculation). We estimated with good precision (i.e. we have narrow 95% confidence interval) a treatment effect on the primary outcome that was around half the magnitude that we declared as being the estimated minimally important clinical difference, and we found a P-value of 0.0558 for this difference. The bulk of the confidence interval [-3.32, 0.04] is in favour of the intervention, making benefit a more likely outcome than harm. Our lower 95% confidence interval at 3.32 rules out our original suggested MCID of 4.21. It would, therefore, seem appropriate to say we have weak evidence of a small effect (<2 units on the NBD measure) and our study has been able to rule out the larger MCID of 4.21. The conclusion could then boil down to a confidence interval that is mostly in favour of benefit but an effect that is smaller than the one the trial was designed to detect. Frequency of defaecation and feeling of more complete emptying are two secondary outcomes specifically mentioned as being of great importance in our interviews and in both we did demonstrate statistically significant improvement in those that

undertook the massage with similar benefits being reported by e.g. the bowel diary and specific questions within the questionnaires.

As identified in the Process Evaluation Chapter, there does, however, appear to be some disparity between the quantitative and qualitative findings. This may be due to the questionnaires being insensitive in this population or could perhaps be a result of interviewees wishing to please the interviewer, or a mixture of the two. The Neurogenic Bowel Dysfunction Score[32] is only validated for bowel dysfunction in spinal cord injured patients. We used this as our Primary Outcome Measure as SCI and MS patients have relatively similar NBD symptoms (only some in MS) correspond to the level of the spinal cord lesions and can fluctuate between constipation and faecal incontinence and may involve slow transit and/or pelvic floor dyssnergia. However, there are also some differences in the pathophysiology of the diseases and approaches to treatment.

Once stabilised and rehabilitated, SCI patients tend to establish a bowel care routine often established whilst in hospital. Their 'disease' does not progress and the bowel symptoms relate to the level of injury. PwMS, on the other hand, have an ultimately progressive disease with many symptoms that can fluctuate in nature and severity. In addition, we do not know all the physiological implications of the disease on the bowel itself or on the neural control of the bowel. For this reason, the NBD score may not have been sensitive enough to detect changes in the symptoms we have identified that matter most to the patient – empowerment and control:

"*I know when I get to the toilet I'm going to have a bowel movement"* (PwMS17).

Our other symptom questionnaire, the Constipation Scoring System[33], is validated in those with chronic but non-neurological constipation and like the NBD uses terms that have been shown to be unfamiliar to the general public: e.g. defaecation, use of drops for evacuation, evacuation, digital stimulation, evacuation of the rectum, constipation, faecal incontinence, flatus incontinence, perianal skin problems. A recent study has suggested that many of these terms are unrecognised by the public[61] and this aligns with some of our incomplete questionnaires in which questions, for example, about digital stimulation were left incomplete either because the patient did not know what this was or were too embarrassed to answer it (information gleaned from nurses' calls). There were also some participants who stated that

completing the questionnaires was very tiring, especially the length of the NBD PROM questionnaire which we were hoping to validate; this again may have attributed to poor or indeed inaccurate completion. Moreover, the EQ-5D-5L[35] results indicated that in both groups MS symptoms worsen over the study period and this may make it difficult to improve one symptom significantly. Following on from our analyses of the NBD PROM questionnaires' repeatability and criterion reliability further work is needed to determine which questions truly reflects what is important to people with MS who have bowel dysfunction.

Throughout the quantitative results, there is evidence of greater improvement in the Intervention Group when compared to the Control Group in the symptoms of incomplete evacuation, infrequency and reduced laxative use (and, therefore, side effects), which were also identified in the interviews. The sensation of incomplete evacuation is a symptom that is rated very common and causes a lot of distress with over 90% of participants indicating this was so:

"Sometimes it would get so bad that I could hardly sit down because I was so bagged up and just couldn't go" (PwMS13).

Data from the bowel diary indicated a significant benefit in this outcome (Mean Change 1.08; 95% CI 0.41,1.76, p=0.002: Table 24 Chapter 3). The response to the individual question in the CSS also indicated a benefit in this symptom (the percentage of participants in the Intervention Group who never felt incomplete evacuation increased from 6.7% at Baseline to 15.5% at Week 24 and in the Control arm from 9.1% to 8.4% (i.e. more in the Intervention are improved) and those who always felt there was incomplete evacuation decreased from 21.3% at Baseline to 3.4% at Week 24 and in the Control group this decreased from 20.2% at Baseline to 10.8% at Week 24. Moreover, the results of the transit study test identified that the markers in the Intervention Group moved more quickly to the distal colon so, if not triggering voiding, could potentially aid evacuation once defaecation was started. Change in stool type could also indicate a possible decrease in transit time with a move towards normal stool types 3 and 4. For example, one participant who mainly passed stool types 1 or 2 prior to the trial every three to four days or more stated:

"*It was just awful. I'd sit on the toilet for ages and ages and ages just knowing that I had to do something and it was painful*" (PwMS17).

By the second stage of interviews, however, she had a bowel movement of stool type 3 or 4 every day:

"*It's back to what it used to be years ago before the MS...really, really quite consistent*" (PwMS17).

The results of stool consistency in the main study as recorded in the bowel diary also indicated a greater percentage in the Intervention Group passing stool type 3, 4 at Week 6, as well as reporting less total constipation at both Weeks 6 and 24 (see Table 13).

An increase in stool frequency was evident from the responses in the NBD, the CSS score and from the bowel diary. This latter outcome was significant (p=0.039) and indicated an increase of .7 stools per week (adjusted change from Pre –Treatment versus Week 6 was 0.5 (SD 1.55) in the Intervention Group and -0.2 (SD1.64); Pre-Treatment V Week 24 Intervention Group 0.4 (SD 1.79) and Control Group -0.2(SD 1.62). In addition, within the repeated measures analysis, the change in frequency of defaecation was significant at Week 6 (odds ratio 0.56 95% CI 0.03 to 1.10; p=0.039); although this effect was decreased at Week 24. It is, however, worth noting that at Baseline the frequency of defaecation in the bowel diary was not that severe with a mean of 3.9 times a week (SD1.71) and the NBD mean score was 8.2(5.2), indicating low to medium levels of constipation - this was also supported in the CSS.

An episode of faecal incontinence can have a devastating impact on a person's self esteem and confidence, creating a reluctance to leave the house and was described by one participant as an 'absolute nightmare' when it happens, especially if out of the house. Faecal incontinence may be frank and unexpected or may be due to the urgency created by the use of laxatives. There was no change in the frequency of faecal incontinence episodes in the quantitative data, but participants in our qualitative study reported decreased episodes and more confidence in leaving the house. Other reported benefits from doing the massage included feeling less bloated, clothing becoming looser and a decrease in sluggishness, with reduced fatigue levels.

Adherence

According to the self-completed diary, recording the frequency of undertaking the massage, adherence to the massage intervention was good: 75% administered the massage 5 times a week; although, interestingly, the vast majority were undertaking self-massage. At Week 24, 66% were continuing with the massage at least 3 times per week. In the qualitative interviews, participants reported that they practised the massage when it fitted in to their routine and altered it according to effect: i.e. they did not necessarily do it every day. In fact, one person felt it to be too effective if undertaken every day.

The adherence to changing lifestyle such as diet and exercise was slightly greater in the Control Group, with 30% (20% in Intervention Group) saying they had made at least one lifestyle change. Such changes may have facilitated the changes reported within the Control Group. The overall uptake of the suggested modifications, supported and discussed at the weekly telephone calls was perhaps lower than expected and is in contrast to what was reported in the qualitative interviews in which the participants said that they found the information to be helpful. To that end, discussing it with the nurse should have aided implementation in both the groups. We did not, however, interview those in the Control Group (a limitation of the study), so have no feedback as to how they felt about the delivery of the advice. It is a recognised feature that for some people with MS, the processing of such information is difficult and requires frequent, spaced re-enforcement.

Who Benefits and why?

Abdominal massage is thought to work by stimulating the bowel and decreasing overall transit time; thus, facilitating defaecation by the stronger propulsion of stools that are less hard and difficult to evacuate. Within our ano-rectal sub-study, it was identified that 60% of this sub-group demonstrated slow transit and if we could extend this frequency of slow transit to the whole study group then it may, to some extent, explain why the response was varied and less than we expected. Patients may also have ano-rectal dyssynergia which can make it difficult to pass stool; if this was the primary reason for their constipation, then abdominal massage would have little effect. However, slow transit and dyssnergia often also co-exist and, unfortunately, due to poor uptake of the follow-up ano-rectal outcomes, we can only speculate and identify this is an area requiring further investigation. Given the small improvement in the primary outcome but not in terms of QUALYs, a low cost version of the intervention might be considered worthwhile by some patients. For example, it could be part of a supported self-management pathway for bowel dysfunction in people with MS. study.

Our data indicate consistently that the male participants reported better outcomes for the Intervention. Although only a small group (n=14 in the Intervention Group and n=21 in the Control Group) the reasons behind these findings are unclear (see Tables 18 and 19). It may be that the male participants were stronger and less fatigued and undertook the massage more effectively. To date, we do not know the amount of force that is needed to be effective in stimulating the bowel. Within our qualitative study, a theme emerged around the adaptations

made due to fatigue and difficulties actually doing the massage; yet there was also a theme that this was something PwMS wanted to do themselves, not to increase care burden and was a way of improving symptoms without taking medications. The amount of pressure and an assistive device to help with self-massage is potentially another avenue that should be explored. There was also some evidence that those with a slightly higher Body Mass Index, slightly older less cognitively impaired with relapsing remitting MS improved more with the abdominal massage. Potentially, the older participants may be retired and have more time; however, why the slightly heavier people should improve more is difficult to explain.

Medication

Constipation was linked to laxative usage, which also could result in negative side-effects. Interviewees reported that taking laxatives caused pain, sleeplessness, cramps and diarrhoea. The unpredictability of passing a stool when taking laxatives meant a number of patients were afraid to leave the house once taken. From the analysis of laxative use, it would seem that those in the Intervention Group are more likely to reduce their laxative use. Participants' overall medication change was monitored and the number of medications seemed to change more in the Control Group; however, this was difficult to analyse as several patients had multiple changes and, in one instance, suppositories were individually mentioned. It was, however, interesting to see the history of the prescribing of laxatives, where it seemed to be the increasing and additional use of different types within a short space of time.

This is an intervention for which we found no evidence of harm and which does not require extensive resources or training. There were a small number of adverse events, none of which could be directly attributable to the massage. Moreover, this is the first time that the reduced training, both to clinicians and participants, was rolled out. In our earlier studies, those teaching the massage to the participants were experienced continence clinicians and the

participants received weekly follow-up visits for support. In this trial, some of the clinicians had no experience of treating either bladder or bowel dysfunction and only one had pre-trial experience with the massage. Feedback from clinicians was very supportive of the intervention and our recruitment is testimony to this. Some reported that further training may have been helpful and this is understandable if a 'hands on' concept was new and also the lifestyle information was not within their usual scope (clinicians ranged from MS Nurses, Continence Nurses, Research Nurse and one research assistant). However, as shown in our Secondary and Sensitivity analyses (see Tables 18 and 19), results were not significantly dependent on sites and the experience of the researchers.

If this intervention was to roll out within the NHS, then we suspect it would depend on local services to facilitate staff training; yet, where these staff sit (e.g. the continence service or the MS Nurse service) is undecided at the moment. Remarkably, there was no feedback from participants that they would have preferred more training or support with the massage. The interviews did highlight that during this initial training, some people preferred the massage to be administered over their clothes or on body parts other than their stomach. This may have affected how the staff member was able to deliver that training, since the massage should be administered on the abdomen in order to allow them to gauge pressure. The clinicians interviewed all remained enthusiastic about the intervention, which influenced the mainly positive feedback participants were giving to them. Those used to treating PwMS recognised that interventions to treat symptoms of NBD are scarce and that this could be part of their 'toolkit' as an adjunct or perhaps instead of, for instance, laxatives, rectal irrigation, biofeedback etc. - none of which are evidence based. Stakeholders also recognised that there was a definite need for additional treatment modalities and that this as a relatively cheap intervention if, after appropriate assessment and training, it is undertaken by the patient themselves or a carer. Additional resources may, however, be required should NHS employees be required to administer the massage routinely.

Limitations

There are several limitations in this study. The differential numbers recruited to our two groups (due to minimisation by centre) coupled with the additional numbers in the Intervention Group who failed to complete the study meant we ended up with a smaller number in the Intervention Group than we had hoped. The extent of missing data and the reasons have been explored but does not seem to be related to any predictable factors. One site UCL which undertook the ano-rectal physiology tests had a slightly lower retention (76.9%) and may have been due to the invasive nature of these tests and unwillingness of participants to return for follow-up. Royal Preston and the Walton Centre both had 81% retention but no specific pattern for loss to follow-up could be identified as reasons were varied and appeared unconnected to the intervention e.g. family illness, moving location.

It may also have been better to use more stringent inclusion/exclusion criteria such as Rome III[70], as some participants were not severely affected (according to the primary outcome measure) by their constipation and therefore had limited capacity to improve. These criteria had been used in a previous study by the authors, but were felt to be too stringent focussing as they do on a clinical expert definition rather than a patient based or a combined clinician-patient definition of constipation. Indeed, the suitability of the Rome criteria for assessing symptoms of constipation has been challenged, as studies show that many patients who report constipation symptoms do not fulfil the Rome Criteria[71-74]. Patient's perception of 'bothersomeness' seemed to fit better. The number of patients self-massaging may also have been a limiting factor due to weakness and fatigue. Several participants in our qualitative study stated some difficulty due to fatigue but tried to work out a way round it by, for example, taking rests. However, for some participants, the massage was probably undertaken at a sub-optimal level. Within our process evaluation study, due to financial constraints, the interviews were only conducted with those who were undertaking the abdominal massage, which poses a limitation on our knowledge on the uptake of the advice and perceptions of taking part in the trial as part of the Control Group. The limitations in the economic evaluation have already been discussed within that chapter.

Future Research

It would seem from the results of the RCT, the qualitative study and the HE component that, similar to other studies, abdominal massage is effective on some patients. Most likely, these would be patients who have primarily slow transit (potentially 60% in this study). Therefore, future research should focus on identifying those with slow transit and, as our ano-rectal sub-study showed, this is not easy to do using invasive tests. There have been attempts tovalidate questionnaires that may indicate which ype of constipation they have: i.e. slow transit and/or dyssynergia and these should first be validated in an MS population and then used for possible screening of those most suitable e.g. Kess Questionnaire.[75] In addition, the optimum frequency and importantly the intensity of massage should be explored with use of pressure sensitive devices and massage devices.

The following is a list of recommendations for future research

1. Further mechanistic evaluation of neurogenic bowel dysfunction and ways of identifying those with predominantly slow transit
2. Further validation of the NBD PROM questionnaire
3. Development of a treatment algorithm which would aid clinicians in the treatment of neurogenic bowel dysfunction
4. Development and evaluation of a device to aid self abdominal massage
5. Development of and clinical trials of other interventions that may help with the symptoms of constipation/faecal incontinence, for example the fruit of the Baobab super fruit which has recently been development in to a drink Baotic

Chapter 7 Conclusion

The benefits of using abdominal massage for the relief of symptoms in people with multiple sclerosis and neurogenic bowel dysfunction are not clearly demonstrated by the results of this methodologically high quality trial, Moreover there is uncertainty around cost-estimates with domination by the control group. The research identified that although the increment in the primary outcome favoured the intervention it was not statistically significant. The analysis of the process evaluation component identified that most (15/20) participants reported benefit and felt it an attractive option as it was non-phramacological and non-invasive. Feedback from clinicians teaching the massage was also positive although in a few cases they expressed concern around the capability of the participant to do the massage effectively. Budget holders, albeit before the results of the trial were known, thought that the infrastructure and training required to introduce abdominal massage as an additional treatment option in this group of patients was implementable.

Based on the results of this program of work we believe that there are some people with MS and NBD who may benefit from undertaking abdominal massage as a low cost self-management intervention, the challenge is to identify these individuals and introduce it as part of a self-management bowel care pathway. Bowel dysfunction is the Cinderella of the continence world with less than 30 RCTs (n=1300 participants)[17] relating to all neurogenic bowel conditions published.

Work such as this should be used to develop a treatment algorithm to facilitate better management of faecal incontinence and or constipation thus improving the lives of patients and their carers.

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Contributions of authors

Professor Doreen McClurg (Chief Investigator and lead grant holder and member of the PMG/TSC) conceived the study, led on the protocol development, analysis and interpretation of the data, and drafting and submitting the final report.

Dr Fiona Harris (Associate Professor, grant holder and member of the PMG/TSC) led and supervised the process evaluation component of the trial and contributed to analysis and drafting of the final report.

Dr Kirsteen Goodman (Trial Manager and member of the PMG/TSC) contributed to the running of the trial, data management, interpretation of results and drafting the final report

Dr Selina Doran (Qualitative Researcher and member of the PMG/TSC**)** conducted the process evaluation data collection and analysis and contributed to drafting the final report.

Professor Suzanne Hagen (Interventions Programme Director (NMAHP research Unit), grant holder and member of the PMG/TSC) contributed to the study design and provided clinical expertise throughout the study and reviewed the final report.

Professor Shaun Treweek (Professor of Health Services Research, grant holder and member of the PMG/TSC) contributed to the study design and provided clinical trial expertise throughout the study and reviewed the final report.

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Professor John Norrie (Chair of Medical Statistics and Trial Methodology and grant holder and member of the AMBER PMG/TSC) contributed to the study design and provided clinical trial expertise throughout the study and reviewed the final report.

Professor Peter Donnan (Co-Director Tayside Clinical Trials Unit and Senior Trial statistician/grant holder and member of the AMBER PMG/TSC) led on the statistical aspect of the trial design, analysis of data and contributed to the drafting and review of the statistical sections of the final report.

Dr Helen Mason (Reader in Health Economics and grant holder and member of the AMBER PMG/TSC) led on the HE aspects of the trial design, interpretation of the data and drafting the HE section of the final report.

Dr Sarkis Manoukian (Health Economist and member of the AMBER PMG/TSC) led on the HE aspects of the trial design, interpretation of the data and drafting the HE section of the final report.

Miss Petra Rauchhaus (Trial Statistician, Tayside Clinical Trials Unit and member of the PMG and TSC) contributed to the trial analysis and reporting of results.

Publication

McClurg D, Goodman K, Hagen S, Harris F, Treweek S, Emmanuel A, …Manoukian s. (2017). Abdominal massage for neurogenic bowel dysfunction in people with multiple sclerosis (AMBER – Abdominal Massage for Bowel Dysfunction Effectiveness Research): study protocol for a randomised controlled trial. *Trials* . 18(150).10.1186/s13063-017-1890-y

Data Sharing Statement

Any data sharing requests to be made to the corresponding author.

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Appendix 1: Massage Training Materials

The ideal position of the participant is supine with appropriate head and knee support, and in a relaxed atmosphere. Adaptations to this position may be required depending on the patient's disability.

There are 4 basic strokes with the massage lasting about 10 minutes.

1. Stroking commences from the small of the back, over the iliac crests, and down both sides of the pelvis towards the groin.
2. Effleurage follows the direction of the ascending colon across the transverse colon and down the descending colon. This is also repeated several times with increasing pressure
3. Palmar Kneading tracks down the descending colon, up the ascending colon, and down the descending colon once again. Effleurage is repeated and continued with a relaxing transverse stroke over the abdomen.
4. Vibration over the abdominal wall to relieve flatus concludes the massage session.

Abdominal Massage Quick reference guide

STEP 1 Stroke upwards to relax the abdominal muscles, in case of hiatus hernia or reflux stroke down.

STEP 2 Stroke from lumbar, to stimulate vagus nerve, which tells the bowel to wake up. Stroke from small of back, round and down inside of iliac crests, finish stroke at groin. Do ten strokes.

STEP 3 Effleurage (toothpaste stoke). Do this in a clockwise direction to stimulate bowel directions to move faecal matter Along. Do this stroke for two minutes.

Heart of Massage, the kneading helps to propel the faecal matter along the colon to load the rectum STEP 4

Palmar Kneading, Descending colon (down pipe) for 2 minutes.

STEP 5 Palmar kneading, up ascending colon (up pipe) for 2 minutes.

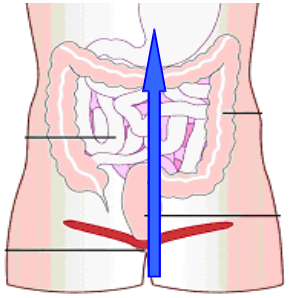
STEP 6 Repeat steps 4 (down pipe) for 2 minutes.

STEP 7 Repeat step 3 for further 2 minutes.

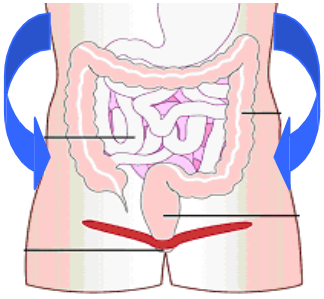
STEP 8 Stroking to relax abdominal muscles and to help body to know the massage is ending. Do this ten times.

STEP 9 Vibrations over umbilicus to relieve flatus (wind). Do this four times.

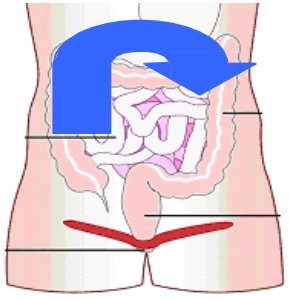
STEP 1 Stroke upwards to relax



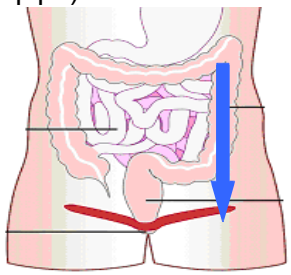
STEP 2 Stroke from lumbar, to stimulate vagus nerve (x10)



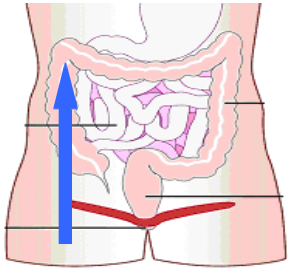
STEP 3 Effleurage (toothpaste stoke) for 2 minutes



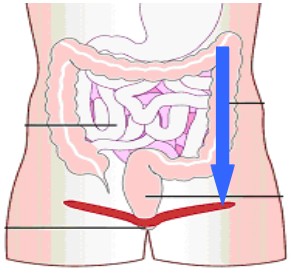
STEP 4 Palmar Kneading, Descending colon (down pipe) for 2 minutes



STEP 5 Palmar kneading, up ascending colon (up pipe) for 2 minutes

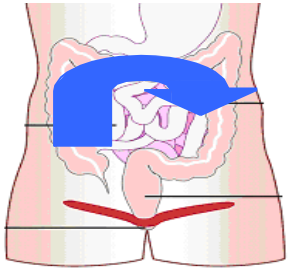


STEP 6 Repeat steps 4 (down pipe) for 2 minutes

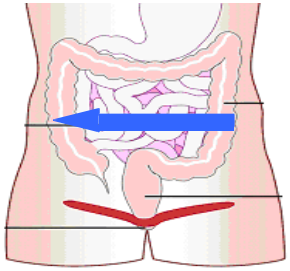


Abdominal Massage Quick reference guide

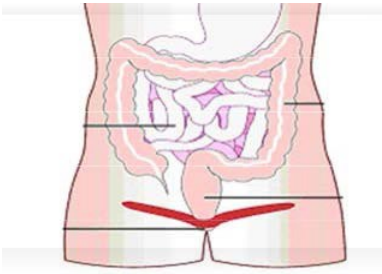
STEP 7 Repeat step 3 for further 2 minutes.



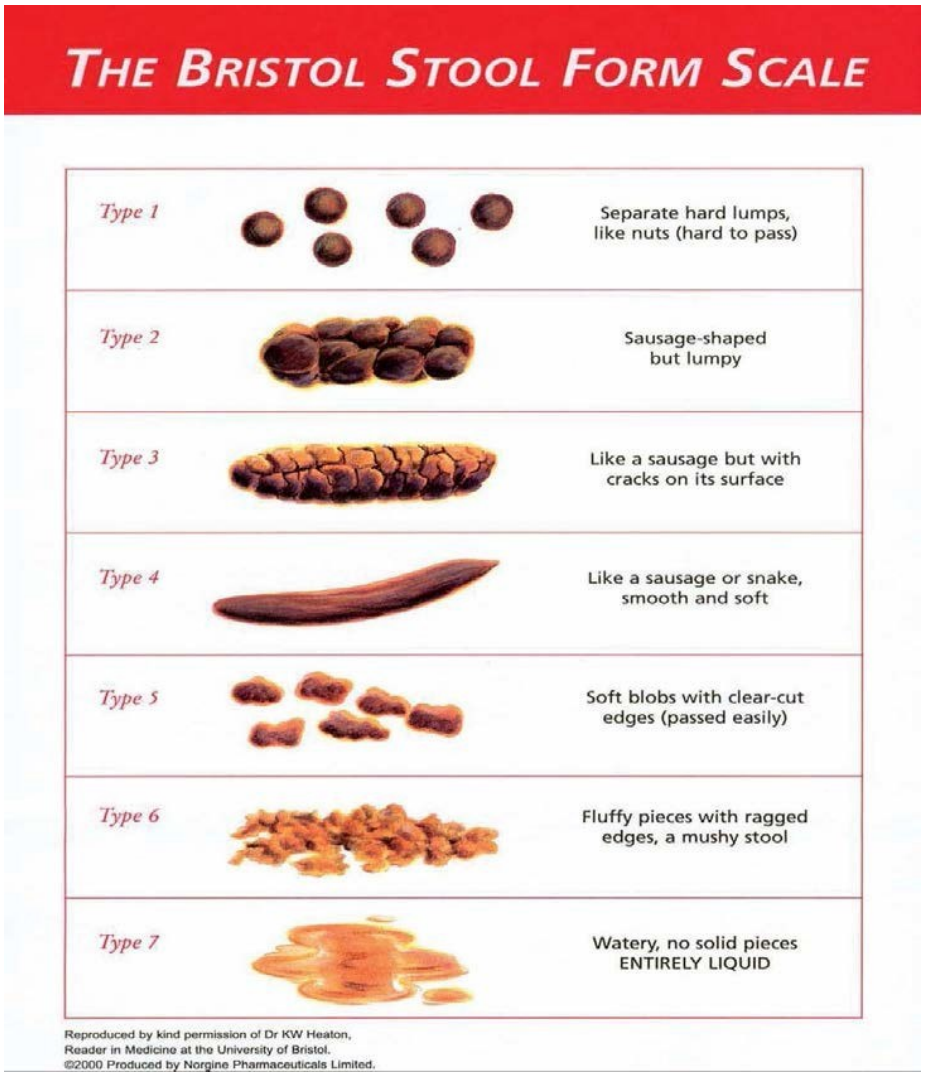
STEP 8 Stroking to relax (x10)



STEP 9 Vibrations over umbilicus (x4)



Appendix 2 Bristol Stool Chart



Appendix 3 Data Monitoring and Ethics Charter

Abdominal massage for neurogenic bowel dysfunction in people with multiple sclerosis

DATA MONITORING AND ETHICS COMMITTEE CHARTER

Funder number	12/127/12 AMBER Appendices Page 247
REC number	14/WS/0111
ISRCTN	**85007023**

Authorised by:

Name: Dr. Chris Sutton Role: DMC Chair

Signature: _____ Date: 21st May 2015

Prepared by:

Name: Dr Doreen McClurg Role: Chief Investigator

Signature: Doreen McClurg Date: 21ST MAY 2015

1.Introduction

The AMBER trial is funded by the NIHR HTA. Research Ethics Committee approval has been given by West of Scotland (ref. no. 14/WS/0111). The sponsors of the study are Glasgow Caledonian University. AMBER trial has been registered on Current Controlled Trials (www.controlled-trials.com, ISRCTN). The Trial Office is located in Glasgow at the NMHAP Research Unit, Glasgow Caledonian University, Glasgow.

1.1.*Trial Objectives*

AMBER is a randomised controlled clinical trial to compare intervention versus no intervention in clinical practice.

1.2.*Scope*

The purpose of the document is to describe the roles and responsibilities of the independent DMEC for the AMBER trial, including the timing of meetings, methods of providing information to and from the DMEC, frequency and format of meetings, statistical issues and relationships with other committees.

1.3.*Facilitation*

The AMBER trial manager will be nominated as a facilitator for the committee. The Facilitator will be responsible for the organisation of the meetings. A summary of each DMEC meeting will be sent to the trial manager for information.

2.Roles and responsibilities

2.1.*Aims of DMEC*

To safeguard the interests of the trial participants, assess the safety and efficacy of the interventions during the trial and monitor the overall conduct of the clinical trial.

2.2.*Terms of reference*

The role of the DMEC is to receive and review information on the progress of recruitment and accruing data of this trial, and to provide advice to the Trial Steering Committee (TSC).
The DMEC should inform the Chair of the TSC if, in their view:

i) The results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that, on balance, one trial arm is clearly indicated or contraindicated for all participants or particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management.
ii) There are significant concerns about patient safety in either arm of the trial.

2.3.*Specific roles of DMEC*

The DMEC's role will include, but not be restricted to, the following:

- monitor recruitment rate and loss to follow up rate
- assess data quality, including completeness of data collection
- define the timing and nature or interim analyses required
- monitor evidence for treatment differences in the main efficacy outcome measures
- monitor evidence for treatment harm (eg SAEs, deaths, complication rates)
- decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups
- suggest additional data analyses
- monitor planned samples size assumptions
- monitor continuing appropriateness of patient information
- assess the impact and relevance of external evidence

6. Organisation of meetings

6.1. ***Frequency***

The DMEC will meet approximately yearly or more often if the DMEC considers it necessary to do so.

6.2. *Attendance*

Effort will be made to ensure that all members can attend. The CI and trial statistician will attend at the request of the Chair. Members who cannot attend in person should be encouraged to participate by teleconference. If, at short notice, any DMEC members cannot attend then the DMEC may still meet if at least two independent members, including the Chair (unless otherwise agreed), will be present. If the DMEC is considering a major action after such a meeting the DMEC Chair should communicate with the absent members, as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMEC.

The meeting report will be circulated at least one week before the meeting in order to enable DMEC members who will not be able to attend the meeting to pass comments for consideration during the discussions at the meeting to the DMEC Chair.

6.3. *Independent members who fail to attend meetings*

If an independent member does not attend a meeting or provide comments when requested between meetings, it should be ensured that the independent member is available for the next meeting. If an independent member does not attend the next meeting or provide comments when next requested, they should be asked if they wish to remain part of the DMEC. If an independent member does not attend a third meeting, strong consideration should be given to replacing this member.

6.4. *Resignation and replacement of independent members due to change in circumstances*

If an independent Committee member's circumstances change (e.g. if he/she moves job to the same institution as the CI) he/she would resign from the committee. A replacement independent member would be identified and appointed.

7.Trial documentation and procedures to ensure confidentiality and proper communication

7.1. *Material to be considered during meetings*

The statistician will provide a report to the DMEC including data to be specified by the DMEC and a short report regarding recruitment progress and any management issues will be prepared by the central coordinating office. This will report on accrual against time and target and any matters affecting the trial.

As a minimum the following information will be reviewed:

- Recruitment to time and target
- A list of reported SAEs
- Any new, relevant or possibly relevant publications identified by the Trial Office
- Interim analyses as specified by the DMEC

7.2. *Accumulating data*

The accumulating study data by arm and interim analyses will be confidential. These will be available to the DMEC. The DMEC will make recommendations in writing to the TSC based on the interim data.

7.3. *Retention of papers after the meeting*

The Chair of DMEC will keep a central record of all minutes, reports and correspondence by the DMEC. Summary reports will be sent to the TSC and Trial office, with any appropriate recommendations. DMEC members will be expected to securely and confidentially retain minutes and reports until the end of the trial. After completion of the trial, confidential DMEC

documents will be archived centrally with the other trial documentation. DMEC member will then delete, or destroy copies of the reports to and from the DMEC, agenda and minutes, as well of copies of communications between meetings. All documentation should be considered confidential.

8. Decision making

8.1 *Possible DMEC recommendations*

Based on review of interim analyses by the DMEC, the possible recommendations to the DMEC could include:-

- No action needed, trial continues as planned
- Early stopping due, for example, to clear benefit or harm of a treatment, or external evidence
- Stopping recruitment within a subgroup
- Requesting an additional interim analysis

The DMEC may recommend unblinding of the TSC to outcome data if a recommendation to stop the trial or recruitment to a subgroup is made.

8.2. *Analysis*

The DMEC should review and agree any interim analysis plan at their first meeting.

8.3. *DMEC decision making methods*

The role of the Chair is to summarise discussions and encourage consensus; therefore, it may be best for the Chair to give their own opinion last. It is important that the implications (e.g. ethical, statistical, practical and financial) for the trial be considered before any decision is made.

8.3. *When the DMEC is quorate*

At least two independent members of the DMEC should be present including the Chair, plus a representative of the trials unit and, if major action is to be considered, the CI.

8.4. *Voting rights*

If a vote is required, all independent members will have a full vote. In addition the CI, or appropriate deputy if CI is unable to attend the meeting, may also vote. In the event of a tied vote, the independent DMEC Chair will have the casting vote.

9. Reporting

9.1 *Communication of DMEC recommendations*

Reports of meetings will be sent to the Chair of the Trial Steering Committee within three weeks of each meeting. A copy will be lodged with the trial office, and also sent to the Chief Investigator. Minutes of the meetings will be kept and signed off by the Chair after each meeting.

A meeting of the TSC will be convened within a few weeks of receipt of the report, to discuss recommendations made by the DMEC. A copy of the minutes of that meeting will be sent back to the Chair of the DMEC.

9.2. *Conflict resolution with other study Committees*

If the DMEC has serious problems or concerns with the TSC decision made in response to the DMEC report, a meeting of both committees should be held. The information to be shown would depend upon the action proposed and the DMEC's concerns. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting.

The meeting would be chaired by a senior member of the central Trial Office or an external expert who is not directly involved with the trial.

10. After the trial

10.1 *Publication of results*

At conclusion of the trial, a copy of the final analysis will be provided to the DMEC chair. He may convene a final meeting of the committee to review this. Names and affiliations of the DMEC members will be included in the trial protocol and the final report. The details of the trial conduct, the results, and the members' involvement in the trial shall remain confidential until 12 months after publication of the final report.

There may be a meeting to allow the DMEC to discuss the final data with the writing committee to give advice about data interpretation.

10.2. *DMEC acknowledgement in publications*
DMEC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise.

Annexe 1: Agreement and competing interests form for independent members

<u>AMBER Data Monitoring and Ethics Committee:</u> Agreement to join the AMBER Trial Data Monitoring and Ethics Committee as an independent member and disclosure of potential competing interests.

Please complete the following document and return to the DMEC Facilitator
(Please initial box to agree)

☐ I have read and understood the DMEC Charter version 1.0, 25th August 2014.

☐ I agree to join the Data Monitoring Ethics Committee for this trial as an independent member

☐ I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that independent members of a DMEC may be biased in some fashion is important for the credibility of the decisions made by the DMEC and for the integrity of the trial.

Potential competing interests should be disclosed via the DMEC facilitator. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent DMEC member should remove the conflict or stop participating in the DMEC. **Table 1** lists potential competing interests.

☐ **Yes,** I have potential competing interests to declare (please detail below)

☐ **No,** I have no potential competing interests to declare

Please provide details of any potential competing interests:

_____

_____

Name: _____

Signed: _____ Date: _____

Table 1: Potential competing interests for independent members

Stock ownership in any commercial companies involved
Stock transaction in any commercial company involved (if previously holding stock)
Consulting arrangements with the Sponsor/Funder
Ongoing advisory role to a company providing drugs and devices to the trial
Frequent speaking engagements on behalf of the intervention
Career tied up in a product or technique assessed by trial
Hands-on participation in the trial
Involvement in the running of the trial
Emotional involvement in the trial
Intellectual conflict e.g. strong prior belief in the trial's experimental arm
Involvement in regulatory issues relevant to the trial procedures
Investment (financial or intellectual) or career tied up in competing products
Involvement in the writing up of the main trial results in the form of authorship

Note: This DMEC charter was developed using MRC CTU template DMEC Charter version 2.01, 13-Mar-2006

Appendix 4 Site and Recruitment Information

Site	Type of facility	Governing Body	Target	Patients Recruited (% Met)	Retention Rate (%)	Abdominal Massage	Standard Care	HCPs involved	Current bowel treatments offered
Anne Rowling Clinic, Edinburgh.	Neurological research facility	NHS Lothian Health Board	10	9 (90%)	9 (100%)	4 (4.4%)	5 (5.1%)	Consultant Neurologist.	None. This site is focused more on advancing MS research.
John Radcliffe Hospital, Oxford.	Tertiary teaching & research hospital.	Oxford University Hospitals NHS Foundation Trust	20	17 (85%)	15 (88.2%)	9 (10.0%)	8 (8.1%)	MS Specialist Nurse; Research Nurse	Bowel problems are under-recognised and only referred to the bowel specialist nurse when explicitly raised.
Leeds County Hospital, Leeds.	Community healthcare service	Leeds Community Healthcare NHS Trust	10	10 (100%)	10 (100%)	4 (4.4%)	6 (6.1%)	Bowel Specialist Nurse; Research Nurse.	Specialised bowel clinics and home visits for those with constipation, faecal incontinence and irritable bowel disorder.
Lincoln County Hospital, Lincoln.	District general hospital	United Lincolnshire Hospitals NHS Trust	10	13 (Exceeded by 3)	13 (100%)	7 (7.8%)	6 (6.1%)	Consultant Neurologist; research nurses.	Advice from an MS Specialist Nurse.
Northampton General Hospital, Northampton.	General, specialist & teaching hospital	Northampton General Hospital NHS Trust	20	14 (70%)	12 (85.7%)	7 (7.8%)	7 (7.1%)	Research & Development Team; Research Nurse; MS Nurse Specialist.	Home visits and a bladder and bowel clinic with bladder specialist nurse and bowel specialist nurse.
Royal Hallamshire Hospital, Sheffield.	Clinical research facility	Sheffield Teaching Hospitals NHS Trust	10	17 (Exceeded by 7)	16 (94.1%)	8 (8.9%)	9 (9.1%)	Research sister; clinical research nurse; consultant neurologist.	Laxatives and diet advice in neurology department.

Royal Preston Hospital, Preston.	District general hospital	Lancashire Teaching Hospitals NHS Foundation Trust	20	22 (Exceeded by 2)	18 (81%)	10 (11.1%)	12 (12.1%)	Senior Research Nurse; Neurologist.	Laxatives, digital stimulation, medication and self-administration of enemas.
Royal Victoria Infirmary, Newcastle.	Tertiary teaching hospital	Newcastle upon Tyne NHS Foundation Trust	20	17 (85%)	16 (94.1%)	8 (8.9%)	9 (9.1%)	Consultant (50% neurology; 50% MS); research nurse.	MS patients only get to see the bowel specialist in Newcastle if there is a significant problem.
Salford Royal Hospital, Salford.	General, specialist & teaching hospital	Salford Royal Hospital NHS Foundation Trust	20	15 (75%)	14 (93.3%)	7 (7.8%)	8 (8.1%)	Research officer; senior research nurse.	Dietary advice from MS specialist nurses. If bowel problems continue, they refer PwMS to colorectal specialists.
Southern General Hospital, Glasgow.	Tertiary referral centre	NHS Greater Glasgow and Clyde Health Board	20	20 (100%)	18 (90%)	10(11.1%)	10 (10.1%)	Healthcare support worker; MS Nurse; consultant neurologist with specialist interest in MS.	MS team can refer to gastroenterology department for them to investigate the problem and offer medication.
The Walton Centre, Liverpool.	Neuroscience centre	The Walton Centre NHS Foundation Trust	20	11 (55%)	9 (81.8%)	5 (5.6%)	6 (6.1%)	Consultant neurologist; research nurse.	Bowel issues are discussed in multidisciplinary clinic and bowel management advice is given.
University College Hospital, London.	National referral & teaching hospital	University College London Hospitals	30	26[1] (87%)	20 (76.9%)	11(12.2%)	13 (13.1%)	Bowel management specialist nurse; gastroenterologist consultant.	This is a specialist bowel centre. Sustainable provision for those with lower bowel conditions: irrigation feedback, pelvic floor physiotherapy, tailored drug regimes, irrigation therapy, surgery and diet advice.

[1]Only 24 of these were included in analysis (2 randomised in error

Appendix 5: Differences in characteristics of missing NBD score at 24 weeks compared to complete data

	NBD Score week 24 present		NBD Score week 24 not present		Total	
Variable	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Intervention						
Abdominal Massage	72	(44.4%)	18	(66.7%)	90	(47.6%)
Standard Care	90	(55.6%)	9	(33.3%)	99	(52.4%)
Total	162	(100.0%)	27	(100.0%)	189	(100.0%)
Centre						
Southern General Hospital, Glasgow	18	(11.1%)	2	(7.4%)	20	(10.6%)
Royal Victoria Hospital, Newcastle upon Tyne	15	(9.3%)	2	(7.4%)	17	(9.0%)
University College Hospital, London	18	(11.1%)	6	(22.2%)	24	(12.7%)
Royal Preston Hospital, Preston	14	(8.6%)	8	(29.6%)	22	(11.6%)
The Walton Centre, Liverpool	9	(5.6%)	2	(7.4%)	11	(5.8%)
John Radcliffe Hospital, Oxford	15	(9.3%)	2	(7.4%)	17	(9.0%)
Leeds Community Healthcare NHS Trust	10	(6.2%)	0	(0.0%)	10	(5.3%)
United Lincolnshire Hospitals NHS Trust	13	(8.0%)	0	(0.0%)	13	(6.9%)
Salford Royal Hospital NHS trust	14	(8.6%)	1	(3.7%)	15	(7.9%)
Sheffield Teaching Hospitals NHS Trust	16	(9.9%)	1	(3.7%)	17	(9.0%)
Northampton General Hospital	11	(6.8%)	3	(11.1%)	14	(7.4%)
Edinburgh (Anne Rowling Regenerative Neurology clinic)	9	(5.6%)	0	(0.0%)	9	(4.8%)
Total	162	(100.0%)	27	(100.0%)	189	(100.0%)
Minimisation criterion						
Walking unaided	66	(40.7%)	13	(48.1%)	79	(41.8%)
Aided walking	76	(46.9%)	13	(48.1%)	89	(47.1%)
Wheelchair bound	20	(12.3%)	1	(3.7%)	21	(11.1%)
Total	162	(100.0%)	27	(100.0%)	189	(100.0%)
Sex						
Male	31	(19.1%)	4	(14.8%)	35	(18.5%)
Female	131	(80.9%)	23	(85.2%)	154	(81.5%)
Total	162	(100.0%)	27	(100.0%)	189	(100.0%)

Differences in continuous characteristics of missing NBD score at 24 weeks compared to complete data

	NBD Score week 24 present	NBD Score week 24 not present	Total
NBD Total score baseline			
N Complete	155	25	180
Missing	7	2	9
Mean (SD)	8.1 (5.1)	8.3 (6.0)	8.2 (5.2)
Median (min – Max)	8.0 (0 -22)	6.0 (1 – 22)	7.5 (0 – 22)
Age [years]			
N	162	27	189
Missing	0	0	0
Mean (SD)	52.8 (10.7)	49.4 (11.3)	52.3 (10.8)
Median (Min – Max)	52.0 (26 – 79)	48.0 (32 – 70)	51.0 (26 – 79)
Duration of MS (years since diagnosis)			
N	162	27	189
Missing	0	0	0
Mean (SD)	14.4 (9.4)	14.1 (8.1)	14.3 (9.2)
Median (Min – Max)	13.0 (0 – 51)	14.0 (1 – 32)	13.0 (0 – 51)
Body Mass Index			
N	157	25	182
Missing	5	2	7
Mean (SD)	26.7 (5.9)	27.3 (5.8)	26.8 (5.9)
Median (Min – Max)	25.8 (14.7 – 48.8)	26.5 (19.8 – 43.9)	25.9 (14.7 – 48.8)

Appendix 6 Summary of Stool type (Bristol stool chart information)

	Intervention Group	Control Group
Baseline		
No stool	39.8%	40.1%
Types 1 & 2	21.8%	18.9%
% constipated	**61.6%**	**59.0%**
Types 3,4	20.2%	17.5%
Types 5, 6 &7	16.0%	19.6%
Missing	2.3%	3.8%
Week 6		
No stool	35.0%	38.8%
Types 1 & 2	22.4%	19.0%
% constipated	**57.4%**	**58.2%**
Types 3,4	29.9%	23.6%
Types 5, 6 &7	11.4%	14.6%
Missing	0.9%	2.4%
Week 24		
No stool	32.0%	41.4%
Types 1 & 2	23.4%	17.5%
% constipated	**55.4%**	**58.9%**
Types 3,4	23.9%	22.8%
Types 5, 6 &7	15.5%	12.0%
Missing	5.0%	5.7%

Appendix 7 Summary of all Adverse Events

Variable	Intervention Group N	(%)	Control Group N	(%)	Total N	(%)
Severity						
Mild	10	(35.7%)	26	(46.4%)	36	(42.9%)
Moderate	14	(50.0%)	23	(41.1%)	37	(44.0%)
Severe (Not Serious)	4	(14.3%)	7	(12.5%)	11	(13.1%)
Total	28	(100.0%)	56	(100.0%)	84	(100.0%)
Causality						
Unrelated	25	(89.3%)	54	(96.4%)	79	(94.0%)
Possibly related	3	(10.7%)	2	(3.6%)	5	(6.0%)
Total	28	(100.0%)	56	(100.0%)	84	(100.0%)
Action taken						
None	14	(50.0%)	22	(39.3%)	36	(42.9%)
Hospitalisation	2	(7.1%)	4	(7.1%)	6	(7.1%)
Medication commenced	6	(21.4%)	23	(41.1%)	29	(34.5%)
Other	2	(7.1%)	2	(3.6%)	4	(4.8%)
Hospitalisation/ meds commenced	1	(3.6%)	3	(5.4%)	4	(4.8%)
Intervention reduced/ Other	1	(3.6%)	0	(0.0%)	1	(1.2%)
Meds commenced/ Other	2	(7.1%)	0	(0.0%)	2	(2.4%)
None/ Other	0	(0.0%)	2	(3.6%)	2	(2.4%)
Total	28	(100.0%)	56	(100.0%)	84	(100.0%)
Outcome						
Recovered	17	(60.7%)	37	(66.1%)	54	(64.3%)
Ongoing	11	(39.3%)	19	(33.9%)	30	(35.7%)
Total	28	(100%)	56	(100%)	84	(100.0%)

Appendix 7 Cont Summary of Serious Adverse Events

	Intervention group	Control group	Total
Breast cancer	1	0	1
Cholecystitis	0	1	1
Fall	1	0	1
Femoral neck fracture	0	1	1
Localised infection	0	1	1
Multiple sclerosis relapse	1	1	2
Myocardial infarction	0	1	1
Urinary tract infection	0	1	1

Appendix 8 Summary of "yes" responses to questions asked during the weekly telephone call (Week 1 and Week 24)

Outcome	Week 1(% Yes)			
	Intervention	Control	Intervention	Control
Diet changed	13.4	19.1	13.1	18.1
Fluid Intake Changed	20.4	27.7	15.5	25.1
Defaecation position changed	25.3	27.7	9.1	8.5
More Exercise	15.1	18.1	12.9	18.8
Con-meds changed	5.7	9.6	15.6	14.9
Use of laxatives changed	13.8	16.0	9.1	15.4
Bowel habits changed	49.4	38.3	42.9	30.9
Bowel habits (more often)	35.6	24.5	29.9	19.1
Bowel habits (less time)	6.9	4.3	18.2	6.4
Bowel habits (less hard stool)	20.7	5.3	20.8	14.9

Appendix 9 Frequency of health care contacts by trial group at Baseline

Service Used	Intervention Group			p
	BR	HR	BR	HR
GP at surgery	0	5	0	6
Nurse at surgery	0	2	0	0
GP on the phone	0	1	1	4
Nurse on the phone	0	0	1	2
GP at home	0	0	0	0
Nurse at home	3	0	1	0
Out of hours clinic	0	0	0	0
Outpatient department	1	3	2	6
Admitted to hospital	0	0	0	0
A&E visit	0	0	0	0
Allied Health Professionals	0	8	0	9
Continence Service	0	0	1	1

Note: Data include all patients that participated in the trial at baseline. There are 90 patients in the Intervention Group and 99 patients in the Control Group. BR refers to bowel problems as the reason to seek help from the health service or come into contact with a health professional. HR refers to other health reasons as the reason to seek help from the health service or come into contact with a health professional.

Frequency of health care contacts by trial group recorded at Week 6

Service Used	Intervention Group			
	BR	HR	BR	HR
GP at surgery	1	15	1	
Nurse at surgery	0	7	0	
GP on the phone	1	7	1	
Nurse on the phone	6	7	11	4
GP at home	0	0	0	1
Nurse at home	10	2	5	0
Out of hours clinic	0	0	0	2
Outpatient department	4	13	1	
Admitted to hospital	0	2	1	5
A&E visit	0	0	0	1
Allied Health Professionals	2	41	0	
Continence Service	3	2	0	2

Note: Data include all patients that participated in the trial at Week 6. There are 60 patients in the Intervention Group and 84 patients in the Control Group. BR refers to bowel problems as the reason to seek help from the health service or come into contact with a health professional. HR refers to other health reasons as the reason to seek help from the health service or come into contact with a health professional.

Frequency of health care contacts by trial group recorded at Week 24

Service Used	Intervention Group		p	
	BR	HR	BR	HR
GP at surgery	7	29	7	42
Nurse at surgery	4	15	1	27
GP on the phone	7	18	2	20
Nurse on the phone	12	0	3	9
GP at home	1	2	1	9
Nurse at home	6	7	14	10
Out of hours clinic	0	0	0	3
Outpatient department	3	20	4	40
Admitted to hospital	1	6	1	8
A&E visit	1	1	0	4
Allied Health Professionals	8	27	14	73
Continence Service	3	3	5	7

Note: Data include all patients that participated in the trial at Week 24. There are 58 patients in the Intervention Group and 83 patients in the Control Group BR refers to bowel problems as the reason to seek help from the health service or come into contact with a health professional. HR refers to other health reasons as the reason to seek help from the health service or come into contact with a health professional.

Total frequency of health care contacts by trial group excluding baseline

Service Used	Intervention Group		p	
	BR	HR	BR	HR
GP at surgery	8	44	8	60
Nurse at surgery	4	22	1	42
GP on the phone	8	25	3	32
Nurse on the phone	18	7	14	13
GP at home	1	2	1	10
Nurse at home	16	9	19	10
Out of hours clinic	0	0	0	5
Outpatient department	7	33	5	67
Admitted to hospital	1	8	2	13
A&E visit	1	1	0	5
Allied Health Professionals	10	68	14	117
Continence Service	6	5	5	9

Note: Data include all patients that participated in the trial excluding baseline. There were 60 patients in the Intervention Group and 84 patients in the Control Group. BR refers to bowel problems as the reason to seek help from the health service or come into contact with a health professional. HR refers to other health reasons as the reason to seek help from the health service or come into contact with a health professional.

Appendix 10 NHS Unit Costs

Service	Unit Cost (£)	Reference
GP at surgery	£44	PSSRU*
Nurse at surgery	£16	PSSRU
GP on the phone	£27	PSSRU
Nurse on the phone	£5	PSSRU
GP at home	£114	PSSRU
Nurse at home	£47	PSSRU
Out of hours clinic	£66	PSSRU
Outpatient department	£117	DH reference costs *
Admitted to hospital	£1,609	DH reference costs
A&E visit	£138	DH reference costs
Allied Health Professionals	£24	PSSRU
Continence (Hospital) Service	£108	PSSRU

Notes: Admitted to hospital refers to the cost of an average impatient stay as estimated in the PSSRU. The cost of £1,609 was applied to each case of hospitalisation assuming an average inpatient stay.

*PSSRU[38] and DH reference costs[39].

Resource use NHS costs per patient by trial group at baseline

	Intervention Group (£)	Control Group (£)
Mean cost per patient	14.59	17.73
Standard Error	4.12	5.12
Standard Deviation	35.41	48.82
95% Conf. Interval	[6.39-22.80]	[7.56-27.89]
t-test on the equality of means	$\|t\| = 0.46$	

Table 32 Notes: Data include all patients that participated in the trial. There were 90 patients in the Intervention Group and 99 patients in the Control Group at Baseline. See Table 31 for NHS services included in these calculations.

Resource use NHS costs per patient by trial group at 6 Weeks

	Intervention Group (£)	Control Group (£)
Mean cost per patient	120.65	186.78
Standard Error	38.01	52.36
Standard Deviation	299.29	485.60
95% Conf. Interval	[44.64-196.65]	[82.67-290.89]
t-test on the equality of means	$\|t\| = 0.95$	

Notes: Data include all patients that participated in the trial. There were 60 patients in the Intervention Group and 84 patients in the Control Group at Week 6. Reported contact with NHS services from baseline to 6 weeks. See Table 31 for NHS services included in these calculations.

Resource use NHS costs per patient by trial group at 24 Weeks

	Intervention Group (£)	Control Group (£)
Mean cost per patient	312.14	313.18
Standard Error	104.45	65.90
Standard Deviation	795.49	600.41
95% Conf. Interval	[102.98-521.30]	[182.08-444.28]
t-test on the equality of means	$\|t\| = 0.01$	

Notes: Data include all patients that participated in the trial. There were 58 patients in the Intervention Group and 83 patients in the Control Group at Week 24. Reported contact with NHS services from 6 weeks to 24 weeks. See Table 31 for NHS services included in these calculations.

Appendix 11 Cost-effectiveness analysis of Abdominal massage versus standard care

		Multiple imputation with a seemingly unrelated regression model	Mixed model
Difference in costs	Mean	50.02	77.54
	SE	156.84	143.8
Difference in QALYs	Mean	-.002	.0026
	SE	.012	.011
ICER	£ per QALY	-19,392.89	28,722.05
Probability of cost-effectiveness at £20,000 per QALY gained		37%	46.6 %

Appendix 13 Notes: ICER refers to incremental cost-effectiveness ratio

Appendix 12 Roles of healthcare professionals interviewed

Type of Interviewee	Interviewees in total	Interviewed in first stage	Interviewed in second stage
-Principal Investigators	6	6	2
-Research Nurse (including those in senior positions)	7	6	6
-General Nurse	1	1	1
-MS Specialist Nurse	3	3	3
-Healthcare Support Worker	1	0	1
-Bowel Management Specialist Nurse	2	2	2
-Research Co-ordinator/Officer/Assistant	5	5	4

Stakeholders selected for interview

Type of Organisation	Aim of Organisations	Interviewees	Expertise of Interviewees
MS Charities	Support and resources for multiple sclerosis patients	2	Policy and research
Incontinence Foundations	Supporting people with continence problems; developing educational and commissioning guidelines	3	Continence service provision; commissioning
NHS Specialist Commissioner	Commissioning support for neurology services in the National Health Service	1	Neurology expertise; policy and research

Appendix 13 Topics discussed during interviews

Intervention Group

First stage at week 4	**Second Stage at end of study**
Personal experiences with MS and bowel problems	Issues faced during first stage
Recruitment into trial	Trial paperwork
Massage training	Weekly nurse calls
Weekly nurse calls	Any other challenges to lifestyle
Trial paperwork	Impact of massage on bowel problems
Administering massage	Unexpected health benefits of massage
Initial impact of massage on bowel problems	Post-trial intentions with the massage
Any problems	Any problems
Advice for other patients/staff members	Advice for other patients/staff members

Topics discussed during healthcare professional interviews

First stage	**Second Stage**
Training delivered by AMBER trial team	Issues faced in first stage
Recruiting participants	Participant recruitment (target met or not)
Training participants in massage	Training participants in massage
Dealing with Control Group participants	Dealing with Control Group participants
Participant follow-up (weekly calls)	Participant follow-up (weekly calls)
Current treatment options at the site	Any problems faced/advice for other sites
Other policy & clinical developments at the site	Implementing the treatment long-term
Any problems faced/advice for other sites	Any problems faced/advice for other sites

Topics discussed during stakeholder interviews.

The organisation's role in neurological and/or incontinence services.
Current policy developments in this area (local, regional and national).
Current treatment options for bowel problems, particularly neurogenic ones.
Whether there a need for an additional treatment option.
The long-term implementation of abdominal massage and any challenges involved.

Appendix 14: Process Evaluation Interview Schedules and Site Questionnaire

Includes;

1. **Draft Interview Schedule: Participant Interviews (First Stage)**
2. **Interview Schedule: Participant Interviews (Second Stage)**
3. **Interview Schedule: Stakeholder Interviews**
4. **Draft Interview Schedule: Health Care Professional Site Interviews (First Stage)**
5. **Draft Interview Schedule: Health Care Professional Site Interviews (Second Stage)**
6. **Six month Site tracking Questionnaire**

Draft Interview Schedule: Participant Interviews (First Stage)

Introduction to the project

1.I'd like to start by finding out a little bit about you (sets context).

Please could you tell me about your life:

Where do you live? Who do you live with?

Are you employed, unemployed or retired? If unemployed or retired, what was your previous occupation?

2.I would now like to move on to discuss your health.

Could you tell me a little about your health:

How long ago were you first diagnosed with MS? Which type of MS do you have and has this always been the case (i.e. it might have progressed into another type)? What impact does this have on you physically (mobility issues, visual, bowel/bladder, fatigue, numbness) and emotionally (cognitive issues, depression, mood swings)?

How do you manage your symptoms (e.g. gentle exercise, sleep patterns, diet, medication, bladder/bowel strengthening exercises)? Have you ever used any non-abdominal form of massage? If so, did this elevate your symptoms and how was this treatment administered (self, carer, nurse)? If not, why not, and would they consider having any non-abdominal massages post-AMBER?

Do you go to any support groups (charities, community groups, friends) relating to MS?

If any experience with bowel problems: You mentioned earlier that you had problems with your bowel – could you expand on this, explaining the difficulties you face and the impact this has on your life?

3.I would like to explore your previous knowledge of abdominal massage

Before you signed up to the AMBER trial, what did you know about abdominal massage as a form of treatment for bowel problems and have you ever used it before the AMBER trial?

If little knowledge and experience, then what are your thoughts on it as a way of managing bowel problems? Is this preferable over alternative forms of treatment (e.g laxatives)?

If knowledge but no experience, then why did you never use it as a form of treatment – perhaps alternative methods were used?

If knowledge and experience, how has AMBER differed from previous massages? Did you find the other abdominal massages worked and, if so, what encouraged you to sign up for AMBER?

4.Now I would like to find out a bit about your experience of taking part in AMBER.

Let's start from the beginning. How did you find the process of recruitment? How did you feel about the treatment before attending your baseline appointment? Did anyone (e.g. relative, friend) attend the baseline appointment with you? Was everything clearly explained to you at the baseline appointment? Is there any way this could be improved?

How was the AMBER training administered and by whom? How do you feel the training went – was everything clearly explained and did you feel you had a clear understanding by the end of it? Is there any way this could be improved?
Will you be administering the massage yourself at home or will someone else? If yourself, how confident were you after the baseline appointment – has this changed at all? If someone else, did they attend the massage training? If yes, do they feel confident after the training? Did they have any suggestions for improvement?

5.I now would like to look at expectations of AMBER when agreeing to take part in the trial.

Why did you sign up for the AMBER study (i.e. expectations about outcomes)? Was anything different to what you expected? Did these outcomes change at any point during the study (baseline appointment, training, after that)?

6.Could we now discuss how you have been getting on with the abdominal massage.

[Based on response to question 4 about who is administering it]: how often have you/they been do this? Do you/they do this at a set time or whenever is convenient? How long does the massage and setting up/winding down take? Is this similar to your other forms of symptom management (i.e. has it been incorporated into a daily routine or is it burdensome)?
Have you altered the massage at all to suit your needs (e.g. using fists to combat fatigue)? Do you feel you/they have a good grasp of the technique? How motivated are you to carry out the massage? Do you have any support when doing the massage or to chat to people about the massage (e.g. local support groups, carer)?

7.May we now discuss whether you have experienced any benefits of doing the massage?

Have you seen an improvement in your bowel functions? If so, in what way (passing stools more frequently and easily)? If not, why do you think this is the case (.e.g. massage not administered correctly, diet, medication, any other factors)?
Have there been any other unexpected benefits (e.g. decreased use of laxatives, more confidence, other physical symptoms)? What impact has this had on your life (e.g. able to go out more, able to eat more, able to engage in another activity like exercise without feeling bloated)?

8.Have you experienced any problems in doing the massage?

[Based on response to question 7 about their success so far with the massage] Have you/they encountered any problems when carrying out the massage? If so, what was the main issue (e.g. pressure to apply, fatigue (if themselves), timing of steps, confusion about massage)? Did you/they devise any solutions to deal with this?
If not, did you believe there would be any problems (e.g. see those above) before undertaking the treatment and, if so, what were related to? Why do you think this has problem has not arisen (e.g. good grasp/adaption of technique, found the right amount of pressure, etc.)? Would you recommend that intervention staff at other sites adopt this lesson in their training?

9.We hope that if AMBER works well for patients, that we might roll this out more widely to help others. Based on your experience so far, is there anything that we could do better?

You have summarised your experience with AMBER so far, is there anything that could be done differently to improve it (e.g. information leaflets provided, training with intervention team, DVD and other training materials, providing more support during the process – telephone calls with nurses in particular, provisions for visual problems and other disabilities)?
Do you think there is anything in particular that could improve the experience for patients who are of a similar age group, as well as the same gender and employment status, as yourself? [Captures demographic details – perhaps there will be different requirements for younger employed females, for instance, compared to older, retired males]

10.Lastly, is there anything that we could do to encourage more MS patients to take part in AMBER?

Earlier we discussed why you were motivated to sign up for AMBER – do you think those reasons would encourage other people with MS to do the same? If not, why not? Do you think there is a way to tackle this issue (e.g. be clearer about what the study involves, provide more incentives to take part)?
[If they stated they keep in touch with other MS patients in their answer to question two] Did you tell your friends/group members about your participation in AMVBER? If so, what were their thoughts about it? Did you try to encourage them to sign up? If not/they declined, why was this the case (do not meet criteria, not enough support in place, unsure about study)?
What about motivation during the study: did you feel engaged and motivated throughout the process? If not, why not (e.g. not enough support, difficulties with massage, etc.)? If this was the case, why did you refrain from dropping out? What would you suggest to encourage completion from other MS patients?

For those interviewed who have 'dropped out'/not completed:
Ask questions 1-5 (modifying as appropriate to their responses) then follow with:
11.I understand that you withdrew early from the study. We would like to learn from you what might have put you off and what we might be able to do better.

Could you please explain why you dropped out the study (e.g. personal reasons, lack of time, problems with study)? If personal/unrelated to study, is there anything AMBER could have done to help you with this? Have you got adequate support in place to deal with this issue? [This is where a recommendation to a support centre for advice might come in]

If directly related to the study, follow up on why they did not feel motivated and engaged with the process: What would have helped with your motivation? How could the level of support provided been improved? What would you recommend to avoid making the same mistakes with future patients of AMBER?

Thank you for your time – we value your input.

Interview Schedule: Participant Interviews (Second Stage)

Pre-amble to the second stage: it will assess what was said in the first stage to see if anything has changed and also to get an overview of their experience with AMBER now they have reached the 24 week stage.

1.I would like to start by looking at your expectations of AMBER when agreeing to take part in the trial.

Why did you sign up for the AMBER study (i.e. expectations about outcomes)? [Add details from first stage about extent of bowel problems.]

Did these outcomes change at any point during the study (baseline appointment, training, 6 weeks, after that)? You said in the first stage of interviewing that you felt the massage was working/not working [delete as appropriate and add details based on perceived impact discussed in first stage of interviewing.] – has this stance changed? How frequently do you visit the toilet now? Did you ever previously have accidents with your bowel, because of urgency in needing to go?

Was anything about the trial different to what you expected?

2.Any problems mentioned last time

[Ask about any problems mentioned during the first stage]. Did any problems occur relating to paperwork or nurse telephone calls or other health problems?

3.In the first stage of interviewing, you shared your experiences of administering the massage:

Did any problems arise that might have impacted upon the effectiveness of the massage [Add details from first stage]

4.Continuing lifestyle changes:

Have you made any lifestyle changes since we first spoke (i.e. more exercise, changes to diet, laxatives, changes to medication)? [Add details from changes made during first stage of interviewing.]

5.Post 6 week AMBER experience?

Last time we spoke, you said you were going to carry on/stop [delete as appropriate] with the massage after the 6 week intervention period – did you do this? If so, please share your experiences on that (i.e. carrying out the massage, but not having to complete bowel diaries and receive weekly telephone calls)? Did this make any difference to your bowel problems? If not, why not and have your bowel problems worsened, improved or stayed the same during this period?

Have you received your 24 week pack? [Due to receive this on the[add date.]] If so, please indicate your thoughts about it. Will you continue to use abdominal massage following your completion of the trial? If so, how often and will you use any measures to track your progress (e.g. keep your own bowel diary)? If not, why and what other form of treatment are you going to use for your bowel problems - would you consider ever using abdominal massage?

Have you got any further questions or comments for the AMBER team?

Thank you for your time – we value your input.

Interview Schedule: Stakeholder Interviews

Introduction

1. I'd like to start by finding out a little bit about you. Please could you tell me about your role as [insert role]?

   I'd like to find out more about the current projects you are involved with [add details based on background research and tailor questions around these.]

2. [Check how much she knows about AMBER beforehand] What do you think the potential might be for self-led abdominal massage to help MS patients with bowel problems? How does this compare to other forms of treatment for bowel problems?

-What kind of savings could be made by patients using self-led abdominal massage (i.e. in terms of not having to see a more expensive staff members like a GP or consultant, reducing nurse contact with patient and chances of hospitalisation)?

Some people with MS are not under the care of an MS service – impact on them?

3. If AMBER proves to be effective for managing bowel problems in MS patients, we would like to take this forward to implement the intervention within NHS contexts. Do you have any thoughts on what might help or hinder that?

Implementing massage

-Could details for the massage be detailed in existing resources, such as guide to bowel problems or 'Making Sense of MS' booklet provided to newly diagnosed patients?

-Which stakeholders/NHS gatekeepers would need to be engaged/involved in the process? [Scottish MS Register, British Neurologists, third sector organsiations?]

-Sustainability: would this be a long-term initative?

-Would it be implemented in MS Trust educational training, e.g. 'MS Nurse Support Programme.'

4. Can you tell us anything about current or forthcoming policies related to the treatment of MS patients that might have a bearing on the rollout of AMBER in the future?

[Add details based on background research pertaining to neurology/continence services based on expertise of interviewee.]

Draft Interview Schedule: Health Care Professional Site Interviews (First Stage)

Introduction to the process evaluation

1.I'd like to start by finding out a little bit your background and your role in the organisation.

Explore their role and involvement with MS: Please could you tell me about your involvement in multiple scleorisis treatment/services? (Amend according to role of interviewee) How long have you been working in this specialist area and at [add name of site]? What does your role entail?

[Add details based on background research.]

Explore the size and location of facility

Could you tell me a bit more about the [add name of site]? Its mission statement is [add from website] – how does this impact your role and the way you treat patients? How is the shift towards consolidating specialist services and working with other specialist centres impacting upon the services offered to patients? Are there any new forms of training being offered to specialist staff?

[Add details about site]

2.How would you describe current difficulties facing the MS patients that come to your centre

Since MS patients can suffer from cognitive and visual difficulties, how does the [add name of site] accommodate patients with speech, visual and hearing problems?

[Add any information available about services.]

3.I'd like to find out about how recruitment of AMBER is going in your area.

Explore how many recruited to Intervention & Control and any barriers or facilitators to recruitment:

First of all, please could you tell me how many have been successfully recruited so far? Could you tell me more about your experience in recruiting these patients (i.e. how did they find out about the study, what convinced them to take part, was the process of sending out recruitment packs, screening and arranging a baseline appointment straightforward, was the information included in the recruitment packs helpful and relevant to the patients)? Did those interested in the study have any questions/concerns before their baseline appointment or wish any additional information to be included in the recruitment packs? Have there been any problems along the way and, if so, what was the cause?

[Patients can be recruited either in clinic or by sending out an **"AMBER Recruitment pack"** to patients who have been screened from notes or a clinic list. The nurse then sends out a recruitment pack to potential patients and, if interested, they return an 'expression of interest' form. The research nurse then telephones the patient to complete the CRF screening; thereafter a baseline appointment is arranged for the patient (either usual time or alternative appointment). The nurse sends out a bowel diary before their baseline appointment.]

4.If we focus now on delivering the intervention itself – what has been your experience of this so far

Explore: how have patients received the information and training; how do staff perceive the intervention:

What have patients reacted to the intervention treatment? Were there any difficulties during the process of administering the massage? Did patients have any questions/concerns about performing the massage themselves? Did patients find the materials provided (DVD, training manual, guide and leaflet) to be helpful and informative or were there any issues? Were there any particular questions about completing the bowel diaries and using the Bristol stool chart?

Now, I want to move onto talk about the experiences of those involved in delivering the intervention. What were your thoughts on the training and materials provided (i.e., was everything clearly explained, were there any problems, any suggestions for ways to improve the training and training materials)? How do you feel about completing the remainder of the intervention (i.e. six weekly telephone calls, 24 week follow-up)?

5.Have you faced any particular challenges in implementing AMBER

Explore challenges and local solutions (changes in staffing; resources; local policy/initiatives):

Does the [add name of site] currently have any treatment options to deal with bowel problems? If so, what does this involve and what challenges arose? If not, why is this the case (lack of funding, specialism in this area, other symptoms take priority)?

Overall, how do you feel about the process of implementing AMBER in the [add name of site] (i.e. challenges involved, what was successful)? With the current financial challenges faced and difficulty in recruiting trained nurses and other forms of clinical staff, are staffing conditions being met?

[Add background research findings.]

6.What do you think has worked particularly well for your centre in terms of implementing AMBER?

Explore local adaptations to the intervention; lessons learned that could be transferred to other teams:

What worked well during the process of implementing AMBER? Did you liaise with any other teams during the process (e.g GPs and community nurses about administering AMBER to those requiring long-term care in their homes)?

Are any additional resources required to successfully implement AMBER? What advice would you give other teams looking to implement AMBER?

7.Are there any other initiatives happening locally for MS patients that might have an impact on our results?

Explore: any local campaigns that might improve recruitment/take-up/completion, or make patients more receptive to self-management etc; other interventions/new treatments being rolled out as part of usual care that might have an impact on bowel problems?

Are there any developments relating to funding, service provision or any local initiatives (such as self-managing symptoms, dealing with bowel conditions) outside the organisation by groups [add names of local and regional groups] that are relevant to the treatment of MS patients? Are there any on-going initiatives, trials and proposed treatments in the [add name of site] or in the local community relating to bowel problems? If so, how would this impact on the administering of AMBER? Are there any charities or other organisations offering support to MS patients?

What kind of psychological and neuropsychological support is provided to patients with MS? Is funding being raised for specific initiatives and, if so, how (private treatment, training levies, fundraising))?

8.To finish, what are the general demographics of MS patients who come to your centre.

Explore: SES range of catchment (deprivation range; urban/rural; ethnicity; age range of patients; if fairly similar to other areas or anything different):

Which groups are most likely to fall into the category of 'did not attend for admission?' Do you think there is a way to change this?

[Add any details found during background research.]

With regards to the catchment area, what are the rates of deprivation, poverty and unemployment? Are these rural or urban places? What is the population of patients with regards to gender, age, ethnicity and unemployment status? Is this fairly similar to other catchment areas within NHS England/Scotland [delete as appropriate]?

Draft Interview Schedule: Health Care Professional Site Interviews (Second Stage)

1. Recruitment

The [add name of site] has currently recruited [add number of participants at time of second stage interview]. Do you think the site will reach its target of [insert number] participants and, if so, do you think it will be able to recruit over this? What advice would you give to other teams in order to recruit successfully?

[Add details of recruitment and any problems faced during first stage of interviewing, including information discovered from interviews with other HCPs at this site.]

There has been [add number] potential withdrawal (check this). Why do you think the site has been so successful/struggled [delete as appropriate] with retention? Have there been any particular problems with patient recruitment and/or retention during the AMBER trial?

[Only ask to those actively involved in recruitment] In the last interview, you were the one been dealing with recruiting patients (e.g. sending out packs, arranging appointments, etc.) – did this continue during the trial or did another member of staff get involved in this?

2. Delivering intervention

Since we spoke last year, were there any difficulties during the process of administering the massage. If so, what impact do you think this would have had on the effectiveness of the massage? If not, did this improve patients' understandings of the pressure required? Did patients have any other questions/concerns about performing the massage themselves? Since you have been carrying out the follow-up calls, how have patients reacted to the intervention treatment?

[Any anecdotes or details mentioned during first stage.]

How has this compared to the reaction of those in the control group? Are you still planning to show the ones in the control group the massage at the end of the trial?

Did patients find the rest of the materials provided (DVD, training manual, guide and leaflet) to be helpful and informative? Have patients had any issues playing the DVD or accessing the videos online?

[Any information provided during first stage.]

Last time we spoke, you said some patients were a bit concerned about completing their bowel diaries properly. Did this continue or what were the reactions of the four other patients you have recruited since then?
How did you get on with the 24 week calls?

I will now move onto any larger changes that may have affected the delivery of the trial. Have there been any changes in staff involved in delivering AMBER in the past six months (e.g. staff leaving or joining the AMBER team)?

What impact, if any, have these changes had on the delivery of the AMBER trial?

Has there been any substantial funding or other changes to your organisation since we last spoke?

3. Problems mentioned during first stage

Mention any problems discussed during the first stage of interviewing – were these resolved?

Are there any other ways to improve the AMBER trial, particularly thinking in terms of an implementation study?

4. Implementing AMBER long-term

Considering your experience with AMBER, do you think it would be possible to implement this as a form of treatment in your centre in the long-term? If not, why not? If so, what additional resources would be needed (staffing, funding, liaisons with external stakeholders)?

Overall, based on your experience of delivering the trial how do you feel about the process of implementing AMBER in the Walton Centre (i.e. challenges involved, what was successful)?

SIX MONTH SITE TRACKING QUESTIONNAIRE

The purpose of this questionnaire is to collect some additional information from the sites involved in delivering the AMBER trial.

It should be completed by the Principal Investigator or their delegate.

Name of Organisation: _____

Name of Staff Member: _____

Date site recruited its first AMBER patient: _____

Date of questionnaire completion: _____

Have there been any new forms of treatment (including treatment for bowel symptoms) introduced to MS patients in your centre/department? YES/NO

If yes, please provide more details e.g. medication, physical therapy, symptom/pain management, any other issues):

How many other trials is your Unit involved in? ☐

How many of these are specifically related to MS? ☐

Are any of these trials related to bowel problems? YES/NO

If yes, please provide more details:

During the last 6 months:

1. *Have there been any substantial funding or other changes to your organisation? YES/NO*

If yes, please provide more details:

What impact, if any, has this has on the delivery of the AMBER trial?

2. *Have there been any changes to care pathways in your organisation and the local area, which could affect MS patients?* YES/NO

If yes, please provide more details (e.g. the primary and secondary services patients can access, social care and community health services, etc.):

3. *Have there been any changes in staff involved in delivering AMBER in the past six months (e.g. staff leaving or joining the AMBER team)?* YES/NO

If yes, please provide more details:

What impact, if any, has this has on the delivery of the AMBER trial?

4. Have there been any particular problems with patient recruitment and/or retention during the AMBER trial? YES/NO

If yes, please provide more details:

Thanks very much for your time. Please return either by email to AMBER@gcu.ac.uk or post to the AMBER Trial Office.